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WHAT THERAPY MEANS.

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Therapy is not a sufficiently studied subject. Books on practice are very generally indefinite and rarely explain the details of treatment, unless it be that of an antitoxin or other brilliant specific. Most teachers of clinical medicine, though brilliant in diagnosis and learned in pathology, glide over the therapy of disease. Hospital teaching is of necessity concerned with serious or unusual ailments and terminal conditions of chronic disease. Even the acute illnesses, such as typhoid fever, pneumonia, and the acute infections, which reach the hospital, occur in a class of people who are very different from those seen in private practice, and in the latter the treatment and management must be very different from that carried out in the hospital. Or, if the patient is found among the poorer classes and in a poor home, and he will not go to the hospital for treatment, again the management of the case must of necessity be very different from that learned by the hospital interne.

A large number of the most common illnesses, all of the serious conditions in their incipiency, and during the possible prevention period a large number of psychic, neurotic, hysterical, functional, glandular, blood, muscle, joint, and nerve disturbances must all be treated by the practising physician, but are never seen in the hospital, and not very satisfactorily in the dispensary.

Hence the above facts, and they are facts, necessitate a continuance of didactic teaching in therapeutics and in the specialites, as many conditions in the latter class never reach the hospital or

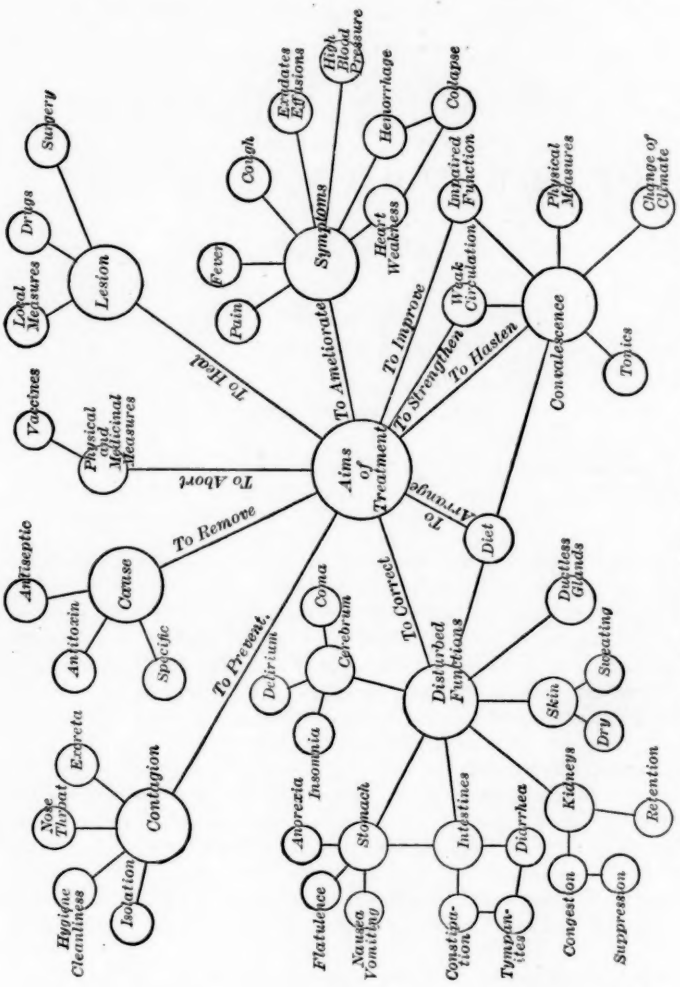

Diagram emphasizing the aims sought in the treatment of any disease or condition.

the dispensary. Clinical surgery alone can be taught only in the hospitals and dispensaries, as a broken leg or an appendicitis are the same in the upper hundred as they are in the lower ten, and the surgical procedures are the same.

While there are a number of most excellent books on therapeutics, they are not sufficiently read, and while we have now long ridiculed the old prescription books and the "drug-alone" treatment of disease, we do not sufficiently teach the larger subject of therapy in most of our medical schools, nor does our best medical literature contain enough of good therapy.

To stimulate a more thoughtful consideration of the duties of the physician who is requested to take charge of a patient, and as a basis for instruction in therapeutics to medical students, I have devised the scheme here presented. The object of this diagram is to emphasize the following aims of the treatment of any disease or condition:

1. Not to forget to use every means to prevent the spread of the contagion and the infection of others if the disease is contagious. If the disease is not contagious, the general hygiene and care of the secretions of the nose and mouth and of the excreta are always of more or less importance.

2. If the cause of a disease can be removed or actively combated, that is the part of the treatment that takes precedence of all others.

3. If the disease, or its localization, or its lesion, or a simple condition, as a cold or a headache, can be aborted, that is another primary object of treatment. The direct treatment of the cause (antitoxin, etc.) may do this, or local measures, as ice, heat, hyperemia, leeches, purges, simple surgical measures, etc., or various drugs may so act as to prevent, control, or abort an impending lesion or functional disturbance.

4. A lesion having occurred the patient will not be well until it has disappeared, resolved, or been removed, and hence as soon as a lesion has been established it is the aim of all of our science to eradicate it. Time and nature's own antagonistic and recuperative powers may unaided accomplish this object, but very frequently we can aid and hasten nature's processes by various means. Frequently only surgery can remove a lesion. At other times a lesion becomes permanent and the patient is permanently damaged to that extent. He may be apparently well in spite of this defect or he may be well as long as he so modifies his food, life, and activities; or he may be an invalid; or the lesion may be the cause of his death, sooner or later. However, in any of these eventualities the treatment or management of the lesion and its pathological results is the main object of treatment.

5. Whether or not the lesion can be successfully treated, objectionable or disturbing symptoms must be stopped or ameliorated. No one but the consultant and text-books can refuse to treat symptoms; the practising physician must and should treat the symptoms. The banal phrase of "symptomatic treatment," pointed at with the finger of scorn, must be now recognized as of great

importance under the new name of the "necessary treatment of symptoms." Pain cannot and must not be suffered, lest cardiac depression and exhaustion occur. High, prolonged fever must be reduced, not every little temperature. Too high blood-pressure must be combated, and circulatory failure must be guarded against and combated when present. Almost all acute disease will cease and the patient will recover, provided we can sustain his heart. It is the heart age. The heart fails and the patient dies even before we have got well into our fight against the disease. We have come from the bleeding, vomiting, purging, starving age, through the aconite and alcohol ages, to the feeding and strychnin age. All showing the change of heart both in ourselves and in our patients. Now too much strychnin is given.

6. Students are not sufficiently taught, and the practitioner does not often enough consider the disturbances of function due to, or caused by, the disease that is present. Medical students are so engrossed in the pathology, differential diagnosis, prognosis, and specific treatment, if there is any, as to get the whole idea of the subject under the caption of "the disease," instead of under the caption of "the patient who has the disease." Hence the patient himself and his disturbed physiology or disturbed functions are forgotten, to his detriment. Just what functions may be disturbed, of course, depends on the disease, the lesion, and the prominent symptoms, but it is an axiom that disturbances will occur, and they should be corrected if possible.

The life processes must go on in illness as they do in health, nutrition must be kept up, excretion must occur, repair by sleep must take place, and the organs concerned in these life processes must be coaxed into the greatest efficiency possible with the handicap that they are enduring.

7. The diet must of necessity be modified by the intensity of the illness, the character of the illness, and the condition of the organs of digestion. The food and drink must always be carefully considered, regulated from day to day to meet the conditions, and then gradually increased during convalescence, or perhaps be modified by a lesion that is permanent.

8. Of course, we wish to hasten convalescence, but have we always carefully enough studied our partially healed patients to scientifically decide just what rapidity in the complete recovery we should expect? Generally we have not done so.

A too low systolic blood-pressure, below 105 mm. in an adult, should prohibit his sitting up and certainly his attempting to walk. Too many long, tedious heart weaknesses from strain occur after operations and after severe illnesses because patients are allowed to get up too soon. The appendix patient up and out in ten days is a cardiac and abdominal risk that should not be advocated.

Again, all physical means of massage, graded exercise, fresh air, change of scene and of climate, or location at least, should be considered in hastening recovery and making that recovery complete.

Unfortunately most all charitable hospital and sanatoria patients are sent home too soon. The lack of means makes this a necessity. If some of the charitable and peace funds that are sent abroad were diverted to our own hospitals there would be less suffering, fewer poor, and less excuse for almshouses, orphan asylums, insane institutions, and public charity as a whole.

THE TREATMENT BY SPLENECTOMY OF SPLENOMEGALY WITH ANEMIA ASSOCIATED WITH SYPHILIS.

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When marked splenomegaly is associated with a history of syphilitic infection or with definitely positive Wassermann tests, a question arises as to the etiological relationship of syphilis to splenomegaly. It is probable that splenic anemia may occur in a patient who has had syphilis in whom it cannot be demonstrated that the syphilis is a definite factor in the condition; on the other hand, it would seem quite proper to separate from other forms of splenomegaly those cases in which syphilitic cirrhosis of the liver exists, gummata of the liver are present, or repeated positive Wassermann tests together with other evidence of infection are obtained.

The grouping of cases should be "away from" splenic anemia in order that every endeavor be made to arrive at as accurate a diagnosis as is possible. Cases classified as splenic anemia should quite definitely conform to that syndrome. By carefully distinguishing the other diseases that are associated with splenomegaly our knowledge will be advanced. Hemolytic jaundice, the portal and biliary cirrhoses of the liver, chronic septic splenomegaly, the splenic anemia of infancy (von Jaksch's disease), endotheliod splenomegaly (Gaucher's disease), lymphoma and lymphosarcoma are the more important entities that have been, and are at the present time, confused with splenic anemia; and in some cases differentiation is impossible even after a study of the pathology. Similarly, cases of splenomegaly in patients with syphilis are to be carefully studied in order that they may be properly classified.

Osler[1] records 3 cases of syphilis with the picture of the Banti type of splenic anemia. Two of these came to autopsy. One a

boy, aged eleven years, had been under observation for four years before death. A greatly enlarged spleen and a scarred cirrhotic liver containing several small gummata were found. The patient had had hematemesis, and presented nodes on the shin, a syphilitic arthritis, and ascites. The Wassermann test was negative and a secondary type of anemia with leukopenia was present. The second case was that of a woman, aged twenty-two years. A scarred liver, ascites, and a severe anemia were present. There was no history of acquired syphilis, and the case was seen before the days of the Wassermann test. The third case occurred in a man, aged thirty-four years, who came neither to operation nor autopsy. There was a history of syphilitic infection. A severe anemia was present, the liver seemed to be fissured, and the spleen extended to the level of the iliac spine.

Anderson,[2] Caussade and Levi-Franckel,[3] and Queyrat[4] have reported in all 3 additional cases simulating the Banti type of splenic anemia. These patients were all definitely syphilitic. None of them were operated on, but one came to autopsy.

Diffuse, *non-gummatous hypertrophy* of the spleen quite frequently occurs in patients with syphilis. In adults it is often associated with gummata of the liver or a definite cirrhosis. *Gummata* of the spleen may be miliary or solitary in character. *Gummatous cicatrices* cause a greatly enlarged organ, and *amyloid spleen* has been found in chronic cases. Moxon[5] has reported a case of *acute splenitis* associated with syphilitic pneumonia, a finding which is evidently exceedingly rare.

Enlargement of the spleen in early syphilis is probably quite common. Wile and Elliott,[6] in a review of 100 cases of early syphilis, found 36 with palpable spleens. In none of these cases was enlargement of the liver present. Splenic enlargement in early syphilis usually tends to disappear, but may persist longer than any other visceral manifestation.

Syphilitic splenomegaly during the first eighteen months of life, and especially during the first three months, is common. From two years to twelve years of age, undoubted cases are relatively rare. Up to the age of six months, splenic enlargement appears in 40 per cent. of syphilitic babies. Carpenter,[7] in a review of 348 cases of splenomegaly in infants and children under twleve years of age, found 57 cases of undoubted syphilis with enlargement of the spleen. He concluded that syphilis was second only to rickets as a cause of splenomegaly in infancy.

Hutchinson,[8] in a report of 22 cases of splenic anemia of infancy (von Jaksch's disease), found 4 with congenital syphilis. Weller[9] in a report of 30 cases of the splenic anemia of infancy found 8 to be syphilitic. Syphilis in infants may be associated with blood findings similar to those of the splenic anemia of infancy just as in adults it may be associated with blood findings similar to those of the adult

type of splenic anemia. This difference in the blood picture is probably due to a peculiar reaction of the infant's hemopoietic system to disease (Giffin[10]).

Gummatous affection of the spleen is very rare in children and extremely rare in infants. It is usually associated with gummata elsewhere. Still[11] collected 4 cases from the literature and reported 2 cases of his own.

In adults, gummata of the spleen are also of rare occurrence. Still,[11] in 1897, was able to collect only 21 cases from the literature. Martin[12] reported a case in which two or three small gummata were found in the spleen in association with multiple gummata throughout the liver and a marked anemia. It is probable, however, that careful examination of the pathological tissue would show a somewhat greater frequency for gummata of the spleen in adults than now appears on a study of the literature.

It is a striking fact, nevertheless, that in adults as well as in children syphilitic splenomegaly is most frequently of a diffuse, non-gummatous character. It is also well-known that syphilitic splenomegaly may persist or recur in spite of the most active anti-syphilitic treatment. Moreover, the severe secondary type of anemia that is frequently present in these cases may not improve with medical treatment. Because of these facts, splenectomy has been performed in three recorded instances and the results would seem to have justified the procedure.

Coupland,[13] in 1886, reported a case of splenectomy for syphilitic spleen. Two years after operation the patient died following hematemesis. Ascites had been present. Autopsy revealed a scarred liver quite typically syphilitic. Hartwell[14] (1913) performed splenectomy on a patient with a severe anemia of the secondary type and a history of hematemesis. The patient denied the possibility of syphilitic infection, but a Wassermann test was strongly positive. Neosalvarsan, mercuric salicylate, potassium iodide, iron, and arsenic had been administered while the patient's condition became less satisfactory. Splenectomy was followed by very prompt improvement. In two weeks the hemoglobin had risen from 25 to 80 per cent. Pathologically the trabeculæ were thickened and large and numerous follicles having fibroid centres were present. Mention of gummata was not made. French and Turner[15] (1914) removed a spleen measuring 7 x 5 inches, and weighing 18 ounces, from a boy, aged five years, in whom there was a blood count suggestive of the splenic anemia of infancy. A Wassermann test had been positive several times and the patient had received antisyphilitic treatment, with no benefit. The patient was apparently well in two months.

In a general review of 58 cases of splenectomy in the Mayo Clinic (July, 1915), 2 cases were briefly discussed in which marked splenomegaly was associated with syphilis (Giffin[16]). One additional

patient has been operated on since that time. The histories of these three patients would seem to be of sufficient importance and interest to justify detailed discussion.

CASE I (A119102) (Fig. 1).—*Marked splenomegaly; severe anemia; no hematemesis; history of syphilitic infection not obtained; Wassermann, total inhibition; antisyphilitic treatment without definite improvement; splenectomy; treponemata in walls of splenic vessels; excellent health one year later.*

G. H. I., woman, aged forty years; married. First examined November 14, 1914. The family history was negative. She had been married fourteen months and had not been pregnant. She had had catarrhal jaundice at the age of eleven years, typhoid fever at

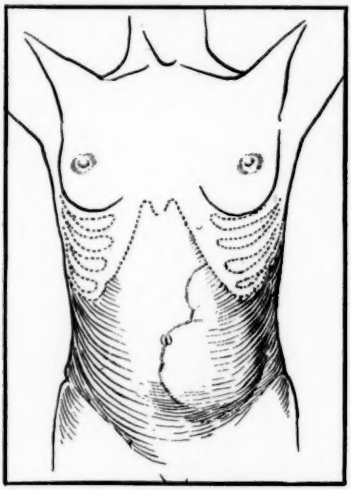

FIG. 1 (A119102).—Position and contour of spleen. Splenomegaly associated with syphilis.

the age of twenty-eight years, and had suffered from many attacks of tonsillitis and quinsy. She stated that her spleen had been enlarged since the typhoid fever twelve years previous; that since that time she had been pale and her complexion had been sallow. As a child, up to the age of fifteen years, she had had an occasional attack of upper abdominal colic without chills, each attack lasting for an hour or two. Four weeks before examination she had suffered from a severe attack of pain in the region of the epigastrium and right costal margin, and was slightly jaundiced after this. There was no history of hemorrhage nor dyspnea, and the patient felt quite strong. There had been a little edema; gastro-intestinal and urinary symptoms were absent. About one year previous to examination a tender swelling had appeared over the anterior

portion of the left chest. This was lanced and later several small pieces of bone were discharged. Six months previous to examination the rib was curetted elsewhere, but drainage had continued up to the time of examination. Antisyphilitic treatment had been administered for six months.

Physical examination disclosed a thin, pale woman; the skin showed a lemon-yellow tint. The weight had been reduced in one year from 130 to 103 pounds. There were small discharging sinuses found in the area of the fifth and sixth left chondrocostal junctures. A large tumor which could easily be recognized as spleen filled almost the entire left half of the abdomen and extended beyond the navel and almost to the symphysis. It was apparently low in position, as its upper pole could be palpated below the left costal margin. The liver seemed to be slightly enlarged on percussion. Examination of the urine was practically negative. The systolic blood-pressure was 106 and the diastolic blood-pressure was 70. Examination of the blood showed a secondary type of anemia, with the hemoglobin at 38 per cent. Red-blood cells numbered 2,950,000 and showed slight anisocytosis. The leukocytes were 6650, and a differential count was not abnormal. Evidence of tuberculosis was not present. A von Pirquet test was negative, and roentgen examination of the chest revealed no pulmonary lesions. A Wassermann test showed total inhibition. On account of the great enlargement of the spleen, and because of the fact that active antisyphilitic treatment had proved unsatisfactory, splenectomy was advised.

Operation, December 4, 1914 (W. J. Mayo). A large spleen measuring 12 x 7 inches and adherent to the diaphragm, stomach, liver and pancreas, was removed through a long left incision. The tail of the pancreas extended up to the hilum of the spleen so that a dissection of about four inches had to be made. The left lobe of the liver was moderately adherent to the abdominal wall, but there was no evidence of cirrhosis. The patient had an uninterrupted convalescence and left the hospital on the eleventh day.

Pathological Report.[17] (L. B. Wilson). Weight of spleen, 900 grams; gland normal in contour, with very marked notch and dorsal groove; external surface slightly nodular; considerable perisplenitis; on section, organ is firm, tough and very dark colored. Microscopically there is a diffuse fibrosis with a moderate lymphocytosis; pulp 3; lymphoid tissue 3; reticulum 3; endothelium of sinuses 2; atrophic pigment 1; amyloid degeneration, 0; arteriosclerosis, 3; adventitia of arteries markedly affected, in some cases amounting to typical gummata; numerous treponemata in vessel walls.

Postoperative Condition. One year after operation the patient's physician stated that she had gained much strength, 15 pounds in weight, and was feeling well. Her blood count was as follows: Hemoglobin, 80 per cent.; erythrocytes, 3,552,000; leukocytes, 11,000. The differential count was not abnormal.

In this case a history of syphilitic infection was not obtained, but a Wassermann test showed total inhibition. The patient was aged forty years, had been married only fourteen months, but had not been pregnant. The spleen was very large and a severe anemia of the secondary type without leukocytosis was present. The liver was not cirrhotic; there had been no hemorrhges. Antisyphilitic treatment had been attended with unsatisfactory results, while splenectomy was followed by prompt improvement and excellent health one year later.

CASE II. (A125899 (Fig. 2).—*Moderate splenomegaly; marked anemia of the secondary type without leukocytosis; liver contained palpable gummata; no hematemesis; negative history of lues in both patient and husband; Wassermann test, total inhibition; no improvement of anemia on antisyphilitic treatment; splenectomy; prompt improvement in general health and blood.*

H. S. D., a woman, aged thirty-two years; married; was first examined March 6, 1915. The family history was negative. For the last ten years menstruation had occurred irregularly, from one week to three months apart. Several hemorrhages occurred which her physician had interpreted as miscarriages. She had had scarlet fever at nine years of age, pneumonia at eighteen years; frequent attacks of tonsillitis as a child. Tonsillectomy had been done at the age of fifteen years. The patient complained chiefly of upper abdominal pain and profuse and irregular menstruation. She had been more or less of an invalid for ten years. Her complaints had been quite varied and often of an obscure character. There was a history of chills at frequent intervals. She had taken large quantities of quinin, but plasmodia had never been demonstrated in the blood. There had been frequent attacks of bronchitis, with evening fever and night-sweats, and she had been treated for tuberculosis, although there had never been positive evidence of this disease. For seven or eight years a cramping of the muscles had recurred in various parts of the body at frequent intervals. For the past five or six years soreness and tenderness had been present in the upper abdomen, at times causing considerable complaint and aggravated by pressure. She had never had an acute abdominal colic. The sensitiveness over the upper portion of the abdomen had been more pronounced for six months prior to examination. She had not known that the liver and spleen were enlarged.

Physical Examination. The patient was moderately thin and anemic. Examination of the heart and lungs was negative, and stereoscopic plates of the lungs failed to disclose any evidence of tuberculosis. The liver extended two inches below the right costal margin and hepatic dulness measured about six inches in the right mammillary line. In the epigastrium two irregular masses could be seen to move downward with respiration. These were easily palpable and apparently located in the liver. The spleen was

enlarged to the level of the navel and its surface was smooth; splenic dulness measured 9 x 17.5 cm. Abdominal fluid did not seem to be present. There was extreme tenderness to palpation over the entire upper abdomen. Examination of the urine was negative. The systolic blood-pressure was 126 and the diastolic 86. An examination of the blood showed a hemoglobin percentage of 50. The red-blood count was 4,090,000; the leukocyte count 6200; the differential count was not abnormal. A Wassermann test showed total inhibition and was repeated with a positive result.

The patient remained under observation for one month, during which time she received three injections of neosalvarsan, and mercurial inunctions and potassium iodide. She gained somewhat

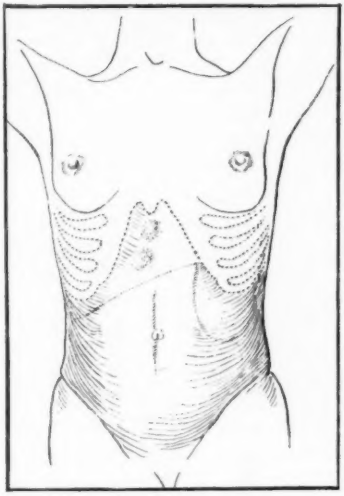

FIG. 2 (A125899).—Position and contour of spleen and liver. Splenomegaly associated with syphilis.

in strength and 7 pounds in weight. The hemoglobin, however, remained low (58 per cent.) and the size of the spleen was not reduced although the liver seemed to be smaller.

Operation. Splenectomy was decided upon and performed April 1, 1915, by W. J. Mayo. A spleen weighing 670 grams, and measuring 9 x 6 inches and quite adherent was removed through a left lateral incision. There was a small amount of free fluid present in the abdomen. The liver showed extensive cirrhosis. Gummatous tumors were present and the liver was divided into large lobes by irregular contractions. The liver was approximately three-fourths normal size. The tumors were typically gummatous in character, and one the size and shape of a gall-bladder was present in the left lobe.

Pathological Report (L. B. Wilson). Weight of spleen, 670 grams, gland long and slender: no notch; slightly roughened surface; considerable perisplenitis; on gross section organ is pale and firm, but not tough. Microscopically there is a moderate diffuse fibrosis; pulp, 2; lymphoid tissue, 2; reticulum, 3; endothelium of sinuses, 2, swollen; pigment, 0; small amount of amyloid degeneration; arteriosclerosis, 2.

Postoperative Course. Recovery from the immediate operation was uneventful and the patient was discharged from the hospital on the twelfth day. Eight months after operation the patient had improved markedly in weight and strength and the anemia had disappeared.

This patient presented a very irregular and indefinite history. Positive evidence of luetic infection could not be obtained, but the Wassermann tests were strongly positive. The spleen was moderately enlarged and non-gummatous. The liver contained palpable gummata. The anemia was marked and of a secondary type without leukocytosis. There was no history of hemorrhages. Active antisyphilitic treatment for one month caused no improvement of the anemia while splenectomy was followed by very definite improvement.

CASE III (A140128) (Fig. 3).—*History of syphilitic infection at twenty-one. Three positive Wassermann tests elsewhere during the last two years; Wassermann test negative at the time of examination; moderate splenomegaly; slight anemia; recurrent hematemesis; long continued antisyphilitic treatment attended with only partial relief; splenectomy. One gumma and a few treponemata in spleen; excellent condition three months later.*

H. P., male, aged thirty-five years; single. Examined September 2, 1915. Family history negative. The patient had had a preputial sore at the age of twenty-one and three attacks of gonorrhea. There was a negative history for other severe diseases. Six years previous he had been jaundiced for two months and thinks the skin had never entirely cleared after that time. He had gradually lost weight from 210 pounds to 170 pounds and had not had his former good general health. Two years previous to examination an ulcer had formed on the right shin. A large spleen and a very large liver were discovered two years before examination. The hemoglobin was 60 per cent. At that time he was complaining of left-side headache, usually worse from 4 to 10 P.M.; pain in the left arm and left leg. Several nodules formed in the left frontal region. From one to three times a week he had severe chills. One and a half years previous the pain in the head, arm and leg were so severe that morphin was necessary. At this time there was an effusion into the right knee-joint. Salvarsan was given; about two days later a severe attack of hematemesis resulting in unconsciousness occurred; after recovery from this his pain had disappeared. Since that time

salvarsan intravenously and mercury intramuscularly had been administered. His general health was then quite good until eight months before examination, when a second severe gastric hemorrhage occurred. This had been followed every two or three weeks by nausea and black stools.

Physical Examination. The patient was well nourished and weighed 173 pounds. The left frontal region of the skull was irregularly depressed. The spleen filled the entire left upper quadrant of the abdomen and was smooth; liver dulness was apparently not increased. A notch of the spleen was palpable while the edge was indefinite. Scars were present on the right shin. Examination of

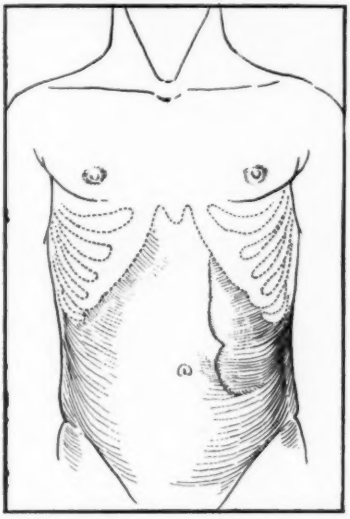

FIG. 3 (A140128).—Position and contour of spleen. Splenomegaly associated with syphilis.

the urine was negative. The systolic blood-pressure was 118 and the diastolic 72. Examination of the blood showed a hemoglobin of 85 per cent.; red-blood count of 4,240,000; leukocytes, 4900; differential count was not abnormal; coagulation time was five minutes. Test meal showed slight hyperacidity. Fluoroscopic examination of the stomach presented evidence suggestive of duodenal ulcer (duodenum was negative at operation) Wassermann test was negative. Three positive Wassermann tests had been obtained elsewhere during the last two years.

The physician who referred this patient stated that while his Wassermann test had become negative and he had improved to a considerable extent under salvarsan and mercury, on the other

hand improvement reached only a certain point and then his recovery seemed to be at a stand-still. (I am indebted to H. B. Anderson, of Toronto, for complete notes upon this case.)

Operation. Splenectomy was decided upon and performed September 13, 1915, by D. C. Balfour. A spleen five times normal size was removed through a left lateral incision. The liver was small and deeply fissured so that portions of the organ appeared almost like separate masses. There was marked obstruction of the portal circulation as evidenced by the varicosities in the round ligament. Stomach, duodenum and gall-bladder were negative.

Pathological Report (L. B. Wilson). Weight of spleen, 1050 grams; notch distinct, capsule slightly thickened; on section, firm, tough, hard, showing general fibrosis. Microscopically there is an intense diffuse fibrosis, 3; pulp, 2; lymphoid tissue, 1; reticulum, 4; endothelium of sinuses, 2; pigment, 1; amyloid degeneration, 2; arteriosclerosis, 3; affecting principally adventitia; 1 typical gumma near vessel, involving wall; a few treponemata.

Postoperative Condition.—The postoperative course was uneventful save for the appearance of a rather severe capillary bronchitis beginning on the sixth day. As a result of the coughing a resuturing of the abdominal wound was necessary two weeks after operation. The patient was discharged in satisfactory condition four weeks later. A Wassermann test done six weeks after operation was negative. Three months later the patient was in excellent condition with hemoglobin at 90 per cent.

This patient presented a history of syphilitic infection and during the course of his illness had had three positive Wassermann tests. There had been two attacks of severe hematemesis. Marked splenomegaly, and an advanced cirrhosis of the liver, apparently syphilitic, were present. The anemia had been recurrent. Very prompt improvement followed splenectomy.

The three cases of splenomegaly herewith reported are definitely associated with lues. Cases undoubtedly occur, however, in which a luetic history is obtained which seems to have no etiological relationship to the splenomegaly. As an instance of this occurrence, the following brief abstract may be given:

(A89075).—*N. B. S., man, aged thirty-five years, married. Examined August 3, 1913; definite history of syphilis with secondaries ten years previous; onset of present illness sudden with severe hematemesis six weeks previous to examination; recurrence of hematemesis ten days before examination; a third hemorrhage nine days before examination; hemoglobin, 35 per cent.; secondary type of anemia; red-blood cells, 2,410,000; leukocytes, 4900. Marked enlargement of the spleen; ascites; gradual improvement followed by splenectomy.* A spleen measuring 10 x 9 inches and weighing 1030 grams was removed. Microscopically there was a diffuse hypertrophic fibrosis. The liver was of normal size and showed no evidence of syphilitic cirrhosis.

This patient presented a definite history of syphilis followed by active treatment and apparent cure. Ten years later sudden severe hematemesis occurred. Marked splenomegaly with ascites was found. A severe secondary type of anemia and negative Wassermann tests completed the typical clinical picture of splenic anemia of the Banti type. At the time of operation no evidence of syphilitic cirrhosis was found.

SUMMARY. 1. It is probable that the syndrome of splenic anemia and Banti's disease may be present in a patient who has had syphilis, in whom it cannot be demonstrated that the syphilis is a definite etiological factor in the condition.

2. Cases of marked splenomegaly in which syphilitic cirrhosis of the liver, or gummata of the liver, are present, or in which repeated positive Wassermann tests together with other evidence of infection are obtained, should be separately classified and studied.

3. Because of the fact that syphilitic splenomegaly with secondary anemia has persisted in spite of active antisyphilitic treatment, splenectomy has been done elsewhere in 3 recorded cases. Three additional cases of this character are herewith reported.

4. The results following splenectomy for marked splenomegaly associated with syphilis and anemia performed after a trial of antisyphilitic treatment seem to have justified the procedure in these few instances.

5. The 3 cases herewith recorded showed prompt improvement after splenectomy and were in excellent condition three months, eight months, and one year respectively from the date of operation.

REFERENCES.

1. Osler, Wm.: Syphilis of the liver with the picture of Banti's Disease. Clinical Journal, 1914, xliii, 462.

2. Anderson, H. B.: Case of syphilitic splenomegaly resembling Banti's Disease. Canada Lancet, 1914, xlvii, 740–742.

3. Caussade, G. and Levi-Franckel, G.: Un cas de syphilis ayant evolue sous la forme du syndrome de Banti; le syndrome de Banti. Bull. et mem. Soc. med. d. hop. de Par., 1914, xxxvii, 1029–1047.

4. Quoyrat, L.: Syndrome de Banti et syphilis. Bull. et mem. Soc. med. d. hop. de Par., 1914, xxxviii, 296–299.

5. Bernard, L.: A propos de l'origine syphilitique des icteres splenomegaliques. Bull. et mem. Soc. med. d. hop. de Par., 3.s., 1908, xxv, 158.

5. Moxon, Walter: Case of Acute Splenitis (?) in a Syphilitic. Tr. Path. Soc. London, 1871, xxii, 274–276.

6. Wile, Udo J., and Elliott, Joseph, A.: A Study of Splenic Enlargement in Early Syphilis. AM. JOUR. MED. SC., 1915, c. 512–518.

7. Carpenter, George: Splenomegaly in Infants and Young Children. Brit. Med. Jour., 1903, ii, 463–469.

8. Hutchinson, Robert: Some Disorders of the Blood and Blood-forming Organs in Early Life. Lancet, London, 1904, i, 1323–1333.

9. Weller, Carl Vernon: Splenic Enlargement in Infancy and Childhood. Arch. Pediat., 1914, xxxi, 514–524.

10. Giffin, H. Z.: Splenectomy for Splenic Anemia in childhood and the Splenic Anemia of Infancy. Annals of Surgery, 1915, lxii, 679–687.

11. Still, George, F.: Gumma of the Spleen in Children. Trans. Path. Soc. Lond., 1897, xlviii, 205–209.

12. Martin, Walton: Case of Syphilitic Splenomegaly. Med. Rec., 1914, lxxxv, 593.
13. Coupland, S.: Brit. Med. Journal, 1886, i, 1445.
14. Hartwell, John A.: Splenomegaly with Anemia in a Syphilitic Patient. Med. Record, 1914, lxxxv, 593.
15. French, Herbert, and Turner, Philip.: Case of Splenic Anemia Treated by Splenectomy (Syphilis). Proc. Roy. Soc. Med., 1913–14, vii, Clin. Sect., 77–78.
16. Giffin, H. Z.: Clinical Notes on Splenectomy. Ann. Surgery, 1915, lxii, 165–170.

ON THE COMPARATIVE TOXICITY OF MORPHIN AND MORPHIN-NARCOTIN (NARCOPHIN).[1]

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The difference in the pharmacological action of the alkaloid morphin or its salts and the galenical preparations of opium has in the last few years been attracting considerable interest. The explanation of this difference in action, and, in general, the relative pharmacodynamic values of the opium alkaloids individually and in combination with each other, sometimes spoken of as the "opium problem," has been the subject of investigation on the part of various pharmacologists, notably of Sahli,[2] Faust,[3] Bürgi,[4] and Straub.[5] Among the most interesting and important contributions on the subject are those of the last-named observer. Straub and his pupils Hermann[6] and Caesar,[7] called attention to the interesting synergism exhibited by the two principal alkaloids of opium in point of quantity, namely, morphin and narcotin. Narcotin Straub regards as a particularly inert body, yet, when that inactive substance is combined with morphin, he found the properties of the morphin to be many times intensified, or, as he expresses it, "potentiated." Thus, for instance, Straub found that the lethal dose of the morphin-narcotin combination for a white mouse is 0.0025 gm., a quantity much less than that of morphin alone, which is 0.015 gm.

Again, the combination of morphin and narcotin was found to affect the respiration much more efficiently than morphin alone. This synergism of morphin and narcotin Straub regards as responsible for the difference in action between morphin and opium.

[1] This investigation has been endowed by a grant from the Council on Pharmacy and Chemistry of the American Medical Association.
[2] Therap. Monatsh., 1909, No. 1.
[3] München. med. Wchnschr., 1910, Nos. 1 and 2.
[4] Deutsch. med. Wchnschr., 1910, Nos. 1 and 2.
[5] Biochem. Ztschr., 1912, xli, 419. [6] Ibid., xxxix, 216. [7] Ibid., xlii, 316.

His work was criticized by Meissner.[8] Nevertheless, a combination of morphin and narcotin meconates under the name of narcophin was put on the market and is being used by various clinicians. A careful analysis of the pharmacological action of the principal opium alkaloids individually and in combination with each other on various physiological functions, circulation, respiration, etc., has been carried on by the author of the present paper for some time, and some of the results have already been published,[9] and still others are to appear later. In the present investigation the author has attempted, at the suggestion of the council on Pharmacy and Chemistry of the American Medical Association, to determine the relative toxicity of large quantities and the lethal dosage of morphin and morphin-narcotin or narcophin. This was deemed especially desirable, as the lethal dosage of the latter drug has been determined by Straub for white mice only.

Animals Studied. Inasmuch as it is a well-known pharmacological fact that the action of narcotic drugs on various animals shows considerable variation among various species as compared with each other, an effort was made to test the action of the two drugs on a large variety of animals in order that the results might be of greater value for therapeutic application. Accordingly, in the present research the action of morphin and narcophin was observed in the following animals: frogs, fishes, turtles, white mice, white rats, guinea-pigs, rabbits, birds, cats, and dogs.

Purity of the Drugs. The alkaloids used were the purest obtainable on the market, and the percentage of impurities in them was too small to vitiate the results.[10]

Action on Frogs. The effect of narcophin on frogs can perhaps be best understood by bearing in mind the individual actions of the constituent alkaloids morphin and narcotin.

The effect of morphin has been well described by earlier writers and is well known to every student of pharmacology. The action is divided into two stages, the narcotic and the tetanic. On administering a large dose of morphin there is, first, a diminution of spontaneous movement, which is followed by incoördination and more or less narcosis. Following this narcotic stage, in an hour or two, the reflexes become active again and the animal soon develops convulsions, from which it may gradually recover or become exhausted and die.

The effect of narcotin has been clearly described by von Schröder.[11] On injection of this alkaloid we note also two stages, a narcotic and a convulsive one. The narcosis, however, is not

[8] Biochem. Ztschr., 1913, liv, 395.

[9] Macht, Jour. Am. Med. Assn., 1915, lxiv, 1489; Jour. Pharmacol. and Exp. Therap., 1915, vii, 338; and 1916, viii, 1.

[10] See L. E. Warren, Amer. Jour. of Pharmacy, 1915, lxxxvii, 439.

[11] Arch. f. exp. Path. u. Pharmakol., 1883, xvii, 96.

deep and is of very short duration, whereas the tetanic stage is very marked and leads to paralysis and death.

The effect of a combination of morphin and narcotin salts, such as the meconates (narcophin) or others, may be regarded as a summation of the individual morphin and narcotin effects.

On injecting a fatal dose of narcophin (about 1 mg. per gram.) into the lymph sac of a frog we also note a narcotic and a tetanic stage. The narcotic stage sets in more quickly than after morphin alone, and the narcosis is much more marked. It generally, however, lasts a shorter time than the narcotic stage following morphin. The second or tetanic stage soon supervenes, which is of a more violent character than that produced by morphin. The animal is soon exhausted and dies from paralysis of the spinal cord.

The following protocols will illustrate the toxic action of narcophin as compared with morphin. (Experiments 1 and 2.) It will be seen from experiment 2 that 25 mgs. of narcophin (consisting of about 8 mgs. of morphin meconate plus 17 mgs. of narcotin meconate) is much more toxic than 25 mgs. of morphin sulphate administered alone. The combination of morphin and narcotin (narcophin) corresponds in toxicity, therefore, to the same weight of morphin, and is much more toxic than the amount of morphin meconate it contains would be alone. Inasmuch as the average fatal dose of narcotin is about 2 mgs. per gram weight of frogs, the toxicity of narcophin for frogs is equivalent to the arithmetical sum of the toxicity of its two components:

Experiment 1. July 8. Frog, 25 gms.

1.35 P.M. Injected morphin sulph. 25 mgs. in 1 c.c. saline in dorsal lymph sac.
1.40 Slight sluggishness of reflexes.
1.42 Deeper narcosis.
2.00 Deep narcosis.
2.24 Reflexes getting more excitable.
2.40 Convulsions.
2.50 Tetanus followed by paralysis.
2.55 Dead.

Experiment 2. July 8. Frog, 24 gm.

1.36 P.M. Injected narcophin 25 mgs. in 1 c.c. saline in dorsal lymph sac.
1.40 Deep narcosis; no response to touch.
1.45 Hyperexcitable; spasmodic movements on rapping on the table.
1.47 Spontaneous tetanic convulsions.
2.08 Paralyzed.
2.12 Nervous system dead; no response to stimulation.

An interesting observation made in connection with the effect of narcophin on the frog is its action on the heart as compared with that of morphin.

It was noted that morphin is more toxic to the frog's heart when given alone than when combined with narcotin. Thus, after morphin injection the heart was seen to beat feebly and, curiously enough, there was a difference in the rhythm of the beats between the sinus and the ventricle. Heart blocks of 2 to 1, 3 to 1 and 4 to 1 were observed. Narcophin, on the other hand, had no such effect. It caused a slowing of the heart beat, but no heart block, and the heart continued to beat for a longer time than after morphin. The following two protocols will illustrate these phenomena. (Experiments 3 and 4.)

Experiment 3. Frog, 27 gms.

11.45 A.M. Injected morphin sulphate 50 mgs. in 2 c.c. saline in abdominal lymph sac.
11.50 Very little change.
11.53 Distinct narcosis; does not respond well to stimulations of touch, etc.
11.55 No response to rapping on table.
12.05 P.M. Same.
12.10 Still, narcotized deeply.
12.15 Placed on back, cannot turn over; reacts but slightly to touch.
12.18 Spontaneous clonic convulsions.
12.23 Same, chest opened; heart shows ventricle beating feebly.
12.30 Paralyzed. Heart shows sinus beating 40 per minute, ventricle, 10 per minute.
12.34 Venous sinus and auricle contract 36 per minute; ventricle, 9 per minute.
12.48 Reflexes all gone; heart still going.
1.05 Dead.

Experiment 4. Frog, 28 gms.

11.44 A.M. Injected narcophin 50 mgs. in 2 c.c. saline in abdominal lymph sac.
11.50 Narcosis beginning.
11.53 Deep narcosis.
11.56 Beginning hyperexcitability; spasmodic movements and jumping on lightly rapping the table.
12.05 P.M. Beginning paralysis; very toxic.
12.10 Same.
12.15 Paralyzed; no response to stimulation.
12.25 Chest opened. Heart beating well, 16 per minute; no heart block.
12.30 Heart beating forcibly 20 per minute; no heart block.
12.34 Heart beating forcibly 32 per minute; no heart block.
12.48 Heart still beating well.
1.15 Heart still beating well.

Action on Fishes. Fish have not been employed as much in pharmacological experiments as they perhaps should be. They are especially interesting in studying the action of opium alkaloids, as the effect on respiration can be conveniently observed by watching the movements of the gills. Charvet[12] made use of gold fish in an early work on opium alkaloids, and Dreser[13] used them in his work on heroin. Russian pharmacologists often employ large fishes for studying the action of drugs on the circulation of the gills. The comparative action of morphin and narcophin was studied by me on small gold fish, and is illustrated by the accompanying protocols. (Experiments 5 and 6.)

The fish were placed in solutions of the drugs in fresh tap water. It will be seen that narcophin is much more toxic for fish than is morphin. That the synergism of morphin and narcotin is responsible for the increased toxicity of narcophin is evident from Experiment 7, showing the action of narcotin alone. A combination of other salts of morphin and narcotin was found to have exactly the same effect as narcophin.

Experiment 5. June 29, 1915. *Carasseus aureus.*

11.50 A.M. Placed in 0.1 per cent. solution of morphin sulphate.
11.55 Swimming around lively. Respirations 125 per minute.
12.00 M. Movements a little sluggish. Resp. about 100 per minute.
12.10 P.M. Same.
12.13 Same. Respirations 84 per minute.
12.20 Same.
12.30 No change.
1.05 Remains stationary, breathing slowly; taken out and placed in fresh water.
Next day Complete recovery.

Experiment 6. *Carasseus aureus.*

11.50 A.M. Placed in 0.1 per cent. of narcophin.
11.55 Swims about lively. Respirations, 120.
11.58 Quiet; respirations, 48 per minute.
12.00 Lying on side, poisoned.
12.20 Dead.

Experiment 7. *Carasseus aureus.*

3.55 P.M. Placed in solution of narcotin hydrochloride 0.1 per cent.
3.57 No change.
4.00 Lying on side, obviously toxic, breathing very rapid.
4.06 Breathing more slowly; lies still, but from time to time makes sudden convulsive movements.
4.15 Dead.

[12] Die Wirkung des Opiums und seine constituirenden Bestandtheile, 1827.
[13] Pflüger's Archiv, 1898, lxxii, 485.

Experiments on Terrapins. The comparative toxicity of morphin and narcophin for these animals was somewhat different from that observed in fishes. In my experiments I used small terrapins 4 to 5 cms. long. These were placed, like the fish, in dishes with shallow layers of the drug solution. It was found that the terrapins when placed in a solution of 0.1 per cent. morphin sulphate died in two hours. To produce death in the same period of time it was necessary to employ a 0.2 per cent. of narcophin, or morphin-narcotin meconate. Inasmuch as narcophin contains about 33 per cent. of its weight of morphin, it will be seen that narcophin is a little more toxic for terrapins than the amount of morphin it contains would be alone.

Experiments on White Mice. The observations on mice, which were the smallest mammals studied in the present work, were interesting from two points of view, both of which have already been described by Straub and his pupils. In the first place, Straub called attention to a remarkable specific biological reaction to morphin noted in mice. He found that after small doses of morphin the animal's tail passed into a curious stiff condition described by him as a state of katatonia. The tail is bent backward or curled spirally, and remains remarkably stiff in that position for a long time. The minimal dose of morphin inducing such a stiffening of the tail is given by him as 0.01 mg., but he remarks that the dosage varies in different strains of mice. Narcophin was found by Straub to give this reaction in much smaller (0.0025 mg.) doses, whereas narcotin does not give the reaction at all.

The smallest dose of morphin which I found to give the reaction in one strain of mice was 0.01 mg. In the same strain of mice 0.02 mg. of narcophin (=0.006 mg. morphin meconate +0.012 mg. narcotin meconate) gave a distinctly positive result.

In another strain of mice I found 0.1 mg. of morphin and 0.2 mg. narcophin required to give the minimum positive reaction.

In the second place, Straub found that the fatal dose of narcophin for mice was much less than that of morphin. This observation I was able to corroborate in my experiments. It required an average from 10 to 20 mgs. of morphin sulphate to kill a mouse of about 30 gms. weight in from one-half to two hours. It took exactly the same weight of narcophin, in other words, about one-third as much morphin in combination with narcotin, to produce death in the same time. It required from 35 to 50 mgs. of narcotin hydrochloride alone to produce death in about six hours. It is, therefore, apparent that the toxicity of morphin for mice is distinctly *potentiated* by narcotin, just as described by Straub.

Experiments on Rats. White rats were used. The results were somewhat different from those obtained in mice. It was found that 2 mgs. of morphin sulphate per gram weight of rat produced death in about one hour. The same dosage of narcophin proved

also fatal, though after a much longer period of time (over six hours). The toxicity of narcophin for rats, weight for weight, is therefore less than that of morphin. The explanation of this difference is to be found probably in its less depressant action on the respiration. The following two protocols will illustrate strikingly this difference:

Experiment 8. July 8. White rat, 185 gms.

10.50 A.M. Injected intraperitoneally, 75 mgs. morphin sulphate in about 3 c.c. saline solution. Respirations, 140 per minute.
11.05 Deep narcosis; tail stiff. Respirations, 36 per minute.
11.15 Same. Respirations, 32 per minute.
11.25 Eyes bulging, very slow breathing, Respirations, 28 per minute.
11.30 Same. Respirations, 20 per minute.
11.34 Dead.

Experiment 9. July 8. White rat, 109 gms.

11.05 A.M. Injected intraperitoneally 50 mgs. narcophin in about 2 c.c. saline solution. Respirations, 140 per minute.
11.15 Standing quiet. Respirations, 96 per minute.
11.25 Same. Respirations, 84 per minute.
11.30 Narcotized distinctly. Respirations, 64 per minute.
11.35 Respirations improve. Respirations, 80 per minute.
11.40 Respirations improve. Respirations, 88 per minute.
11.50 Breathing about 88 respirations per minute.
12.10 Tail stiff. Respirations, 76 per minute.
12.55 Lies quietly. Respirations, 80 per minute.
1.25 Same. Respirations, 84 per minute.
1.50 Same. Respirations, 72 per minute.
4.50 In good condition. Respirations, 80 per minute.
Next day, found dead.

Experiments on Guinea-pigs. These animals, like rats, were also found to be very resistant to the effects of the opium alkaloids. The injections were given subcutaneously at intervals of from ten to twenty minutes, administering 25 to 50 mgs. of the drug at a time. It was found that the lethal dose of morphin sulphate was on the average about 1.5 mgs. per gram weight of guinea-pig and that of narcophin very much the same, or 1.6 mgs. per gram weight. Six hundred milligrams of narcotin hydrochloride alone administered to a guinea-pig weighing 550 gms. resulted in death on the following day. This made the average lethal dose of narcotin about 1.1 mgs. per gram weight. It will be thus seen that the lethal dose of narcophin is considerably greater than the arithmetical sum of the toxic doses of its two constituents, morphin and narcotin. This lesser toxic effect is probably also to be attributed to its less depressant influence on the respiration. It was found that morphin reduced the respiratory rate from 120 to 48 per

minute, whereas the greatest reduction after narcophin was found from 120 to 88 per minute. Narcotin alone not only did not slow the respiratory movements, but actually deepened and accelerated them. The less depressant action of narcophin thus seems to be due to the synergistic action of its two constituents.

Experiments on Rabbits. The comparative toxicity of morphin and narcophin for rabbits is of especial interest, as many of our posological data for opium alkaloids are derived from experiments on these animals.

The drugs in our experiments were administered in two ways, subcutaneously and intravenously. It was noted that morphin is much more toxic for rabbits when given through a vein, and thus suddenly thrown into the blood stream in large quantities, than when it was absorbed slowly after subcutaneous injections. The average fatal dose of morphin given intravenously was 0.31 mg. per gram weight of rabbit; and when injected under the skin or intraperitoneally also about the same or 0.32 mg. per gram weight, death occurring in the first case in from thirty to sixty minutes, while in the latter only after three or four hours. The fatal dose of narcophin, however, when injected into a vein was found to be about 0.17 mg. per gram weight of rabbit; whereas administered subcutaneously it was 0.79 mg. per gram weight. It was noted that after intravenous injections of narcophin the animals quickly developed very violent convulsions, from which they died. In one case I have seen a 1000 gm. rabbit succumb to 40 mgs. in less than five minutes. These convulsions were also seen after intravenous morphin injections, but were not so violent and did not come on so quickly. After subcutaneous injections, convulsions were not the striking feature after either drug, except toward the end. On the other hand a remarkable difference in the respiratory function could be noted. The breathing after administration of morphin was powerfully depressed, the respirations becoming shallow and very slow, their number in extreme cases decreasing to one-sixth or one-eighth of the original. After narcophin, on the other hand, the breathing was not so much depressed, the number of respirations never falling to less than one-fourth of the original and the individual respirations were often deeper than normally. (Protocols Experiments 10 and 11.)

Experiment 10. July 15, 1915. Rabbit, 1600 gms.

3.35 P.M. Respirations, 200 per minute. Injected 100 mgs. morphin sulphate in ear vein.
3.40 Respirations, 36 per minute.
3.45 Slight convulsions.
3.55 Respirations, 44 per minute. Injected 50 mgs. morphin sulphate.
4.05 Injected 50 mgs. morphin sulphate.
4.15 Injected 50 mgs. morphin sulphate.

4.25 Injected 50 mgs. morphin sulphate.
4.35 Injected 50 mgs. morphin sulphate.
4.40 Injected 50 mgs. morphin sulphate.
4.45 Injected 50 mgs. morphin sulphate; convulsions.
4.55 Injected 50 mgs. morphin sulphate; violent convulsions.
5.00 Death.

Experiment 11. July 15, 1915. Rabbit, 1350 gms.

2.35 P.M. Injected in ear vein 100 mgs. narcophin. Respirations, 200 per minute.
2.45 Deep narcosis; slight convulsions; respirations, 96 per minute.
3.10 Injected 50 mgs. narcophin; respirations, 75 per minute.
3.25 Injected 50 mgs. narcophin; violent convulsions.
3.26 Dead.

Experiments on Dogs. The drugs were administered to these animals also in two ways, viz., intravenously and subcutaneously, and, as was to be expected, the intravenous toxic doses were much smaller than those required for hypodermic injections. The average fatal dose of morphin in saline solution injected slowly into a vein of a dog under ether was 37 mgs. per kilo, death supervening in about two hours. The fatal dose of narcophin administered in the same way was 173 mgs. per kilo. The fatal dose of morphin by subcutaneous injection was 200 mgs. per kilo while that of narcophin was about 310 mgs. per kilo weight of dog. As compared with narcophin, morphin depressed the breathing to a much greater extent, the number of respirations decreasing to one-fourth or one-fifth of the original. Narcophin produced much less respiratory depression, the number of respirations decreasing about one-half; but, on the other hand, this drug produced earlier and more violent convulsions.

Experiments on Cats. Experiments on these animals are interesting more from a pharmacological than a therapeutic point of view, as it is well known that morphin exerts a peculiar action on cats. When that alkaloid is injected into a cat no narcotic action is produced; on the contrary, the drug acts as a delirifacient and convulsant. One interesting observation in this connection is that noted by Straub. That observer claims that a combination of morphin with narcotin acts upon cats as a narcotic; in other words, if narcophin is injected into a cat, or if narcotin is first injected and is later followed by a dose of morphin, no delirium or convulsions are produced, but the animal is narcotized.

I have endeavored to repeat Straub's experiments, but have only on rare occasions observed such a narcotic action. In most cases a combination of morphin and narcotin acted just like morphin alone; that is, as an excitant, the effects being only somewhat delayed. After small doses (10 to 20 mgs. per kilo) the delirium

was perhaps less marked. After large doses of narcophin, however (40 to 50 mgs. per kilo), violent delirium was produced.

In this respect my observations were in agreement with those of Meissner.

Narcophin was furthermore found to be more toxic for cats than the amount of morphin it contains. It was found that 100 mgs. per kilo weight of cat excited the most violent delirium and resulted in death in an hour, whereas a dose of 50 mgs. of morphin per kilo weight of cat also produced violent delirium, but was followed by recovery on the following day. Narcotin alone, injected in quantities of 100 mgs. had no visible effect on the animals. (Experiments 12, 13, 14 and 15.)

Experiment 12. January 25, 1915. Cat, 2.5 kilos.

1.15 P.M. Injected subcutaneously 30 mgs. morphin sulphate.
1.30 Hyperexcitable.
2.00 Violent delirium; frothing at mouth.
Delirium lasts all day.

Experiment 13. January 25, 1915. Cat, 2.5 kilos.

1.00 P.M. Injected narcotin hydrochloride, 60 mgs., subcutaneously.
1.30 No effect; sits quietly.
2.00 Injected 30 mgs. of morphin sulphate.
3.00 Lies quietly.
4.00 Violent delirium and convulsions.

Experiment 14. June 28, 1915. Cat, 2.5 kilos.

1.45 P.M. Injected 100 mgs. morphin sulphate subcutaneously.
2.00 Hyperexcitability.
2.15 Delirium.
2.45 Very wild delirium.
3.00 Delirium continues; mouth frothing.
4.30 Same.

Next day

11.15 A.M. Still hyperexcitable.
2.00 P.M. Getting more quiet.

Experiment 15. June 28. Cat, 2.2 kilos.

11.15 A.M. Injected 200 mgs. narcophin.
11.30 Delirium.
12.00 M. Delirium more violent; foaming at mouth; rolls on back in convulsions.
1.15 P.M. Exhausted from convulsions.
2.45 Dead.

Action on Birds. S. Weir Mitchell,[14] in 1869, called attention to an incidental observation in which he noted the extreme resistance of pigeons to morphin. In connection with the present investiga-

[14] Am. Jour. Med. Sc., 1869, lvii, 37.

tion it was interesting to inquire whether a combination of morphin with narcotin acted in the same way. Accordingly, two pigeons were selected and one received injections of morphin sulphate under a wing, while the other was injected with narcophin. It required 250 mgs. of morphin sulphate to produce death which supervened, preceded by convulsions, in about an hour and a half. Narcophin was seen to produce much more toxic symptoms. The animal made convulsive movements after an injection of 50 mgs. It was paralyzed after 200 mgs., and died in convulsions after 250 mgs. of the drug one hour and thirty-five minutes after the beginning of the experiment.

Discussion. The results of the present investigation may, for convenience of comparison, giving the average minimal lethal dose for each animal, be placed together as in the accompanying table.

TABLE OF COMPARATIVE DOSAGE FOR VARIOUS ANIMALS.

Animals.	Minimal lethal. Dose of morphin.	No. of exps.	Minimal lethal. Dose of narcophin.	No. of exps.
Frog . . .	1 mg. per gm. wt.	12	1 mg. per gm. wt.	18
Fish . . .	0.2 per cent. solution	12	0.1 per cent. solution	12
Terrapin .	0.1 per cent. solution	3	0.2 per cent. solution	3
White mouse	0.5 mg. per gm. wt.	12	0.5 mg. per gm. wt.	12
White rat .	2 mgs. per gm. wt.	3	2 mgs. per gm. wt.	3
Guinea-pig .	1.5 mgs. per gm. wt.	3	1.6 mgs. per gm. wt.	3
Rabbit (intravenous) .	0.31 mg. per gm. wt.	3	0.17 mg. per gm. wt.	6
Rabbit (subcutaneous)	0.32 mg. per gm. wt.	3	0.79 mg. per gm. wt.	4
Cat . . .	Over 100 mgs. per kilo wt.	6	50 mgs. per kilo wt.	12
Dog (intravenous) .	87 mgs. per kilo wt.	4	173 mgs. per kilo wt.	6
Dog (subcutaneous .	200 mgs. per kilo wt.	4	310 mgs. per kilo wt.	6
Pigeon . .	1 mg. per gm. wt.	1	1 mg. per gm. wt.	1

It is well to note that the figures here given are not so much of value as absolute standard toxic or lethal units as giving the relative toxilogical values of morphin and narcophin. The absolute lethal dosage may vary, as is well known, with the strain or breed of the animal used, time of year, etc.; the ratio of toxicity of two drugs, however, performed on two animals of the same lot at the same time remains pretty constant.

It will be seen that the lethal doses for various animals differ enormously, but that in general the fatal dose of narcophin is about the same weight for weight as that of morphin.

Inasmuch as narcophin consists of about 33 per cent. by weight of morphin meconate and 67 per cent. of narcotin meconate, it is obvious that the toxicity of narcophin as compared with the toxicity of the morphin meconate which it contains if given alone is much greater. This greater toxicity can be in some cases, as that of the frog, explained by the arithmetical sum of the effects of its two

components. In other cases, however, the morphin and narcotin seem to potentiate each other, in the sense of Straub.

These observations are of importance from a clinical point of view. Of the clinical observers who have so far published their experiences with narcophin (Klaus,[15] Cassel,[16] Hirsch,[17] Kleinberger,[18] von Stalewski,[19] Jaschke,[20] Schlimpert,[21] Zehbe,[22]), some employed it in the same doses as morphin. Others, however, as, for instance, Hirsch, enthusiastically advocate larger doses, 45 to 60 mgs., as innocuous.

In regard to such dosage we would urge caution. Although within toxic limits narcophin may be perfectly harmless even in larger doses than have been so far employed, still it is well to bear in mind that in comparing the therapeutic values of drugs we should be guided by the ratio of the *dosis lethalis*, or lethal dose, to the *dosis efficax*, or dose sufficient to produce a therapeutic effect. What this ratio is for narcophin in the case of man is still an open question.

It is further apparent that the synergism of morphin and narcotin is highly complicated; the same function responding differently to the combination in different animals. Experiments made on one species cannot, therefore, be made the basis of conclusions for other species; much less so for therapeutic use in man.

In this connection it is interesting to note that the author in conjunction with Herman and Levy has found that the analgesic power of a morphin-narcotin combination is much greater than the arithmetical sum of the analgesias produced by its constituents separately.[23]

Summary and Conclusions. 1. The comparative toxicity of morphin and narcophin was studied on various animals: pigs, fish, terrapins, mice, rats, guinea-pigs, rabbits, pigeons, cats, and dogs.

2. It was found that in general the toxicity of narcophin is about the same as the same weight of morphin.

3. Narcophin consists of one-third its weight of morphin meconate and two-thirds its weight of narcotin meconate. Inasmuch as the toxicity of narcotin is very low, we have here a distinct potentiation of the toxicity of morphin.

4. It is, therefore, not advisable to administer narcophin clinically in doses larger than those of morphin.

[15] München. med. Wchnschr., 1914, p. 186.
[16] Therap. d. Gegen., 1914, p. 186.
[17] Deutsch. med. Wchnschr., 1914, p. 703.
[18] Therap. d. Gegenw., 1914, No. 3.
[19] Ibid., 1912, No. 11.
[20] München. med. Wchnschr., 1913, No. 2.
[21] Ibid., 1912, No. 28.
[22] Ibid.
[23] Jour. of Pharmacol. and Exp. Therap., 1916, viii, 1.

MULTIPLE PRIMARY INTRAVASCULAR HEMANGIO-ENDOTHELIOMATA OF THE OSSEOUS SYSTEM ASSOCIATED WITH THE SYMPTOMS OF MULTIPLE MYELOMATA—A LESION HITHERTO UNDESCRIBED.

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We purpose to describe a lesion of the osseous system attended, by symptoms indistinguishable from those of the multiple myelomata and associated with histological features which combine with the clinical characteristics to form an apparently unknown disease.

Case Report.—The patient, a Russian machinist, aged forty-three years, was admitted to Bellevue Hospital complaining of severe pain in the left gluteal region. The pain extended upward to the tenth dorsal vertebra, but did not involve the lower extremities. The patient stated that the pain had grown progressively worse during the thirteen months previous to his admission to the hospital, that it was burning in character, continuous in point of time, and severest at night. Physical examination disclosed a small, indurated, exceedingly painful mass lying just to the left of the anus. The mass was attached to the tuberosity of the ischium. Roentgenographic examination showed irregularities in the periosteal outlines of the left ischium and signs of infiltration of the adjacent tissues. The corresponding hip joint was intact. In the course of the next two months the patient began to complain of tenderness and pains in the right lumbar region and buttock, in the upper part of the right thigh and in the axillary region of the right side. The manubrium sterni, the upper end of the right humerus, and the upper segment of the occipital bone were similarly affected. In the course of the succeeding five months two tender masses became palpable in the occiput and the movements of the left thigh and right arm grew to be exquisitely painful. Roentgenograms revealed complete absorption of the first rib on the right side and of the left ischium from the symphisis to the acetabulum and infiltration of the soft tissues of the vicinity, together with involvement of the upper end of the right humerus

and fracture of the surgical neck. In the course of a few weeks there were signs of wide-spread destruction of the vertebræ. The patient, who was now anemic and emaciated, had to be kept under opiates for the relief of pain. Eventually he left Bellevue Hospital and died in another institution.

The urine was twice examined for Bence-Jones protein, with negative results.

There was nothing in the clinical manifestations or in the numerous roentgenograms to indicate visceral involvement, with the possible exception of a small cloudy area disclosed by one of the pictures taken of the lower lobe of the left lung.

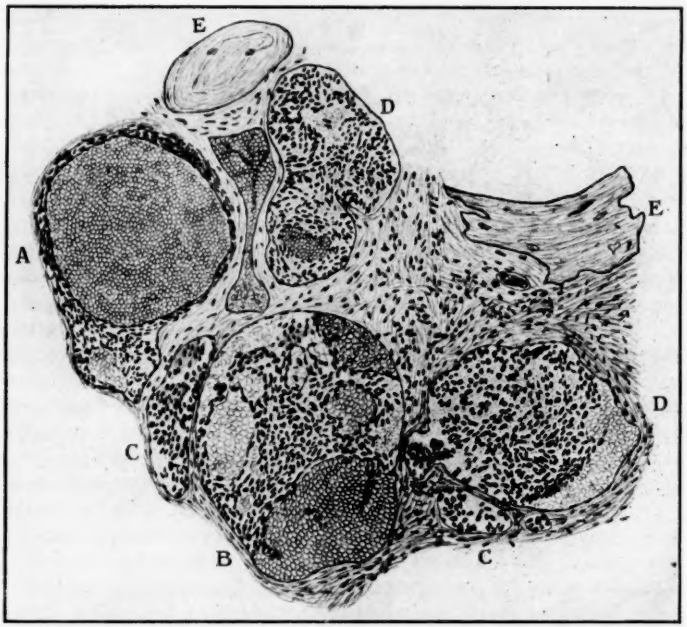
In order to afford relief to the patient the tumor was curetted on several occasions, and, in this way, we were enabled to determine the microscopic changes in the skull, humerus, and ischium.

HISTOLOGY. The unit of the tumor is a thin-walled bloodvessel, lined by a single layer of flattened endothelial cells, the lumen distended by red blood corpuscles, the whole embedded in a stroma of poorly cellular fibrillar connective tissue arranged around spicules of bone. Here and there, however, the lining endothelium may be seen as a uniformly growing circumferential layer from 5 to 20 cells in depth, and from this point the process of proliferation may be followed through various stages leading to occlusion of the lumen by spindle-shaped tumor cells. In other cases the overgrowth of endothelium commences at the periphery of the vessel as one or more arm-like projections and the lumen is eventually occluded. An extraordinary histological feature consists in proliferation of the endothelium in such a way as to subdivide the vascular lumen into one or more compartments filled by red cells, obviously representing an attempt to form new vascular channels

SUMMARY. As far as we have been able to learn from a search of the literature on primary tumors of the bony system the lesion above described is unique. Zetkin,[1] for example, has called attention to a variety of so-called hemangio-endothelioma originating in the region of the diaphysis of the humerus. Not only was the origin a solitary one, but the histology is totally different from that of our tumor, consisting in alveoli of cuboidal cells of the epithelial type associated with numerous large, blood-filled channels embedded in connective tissue. The description of the histology reminds one of the adenocarcinomata or of the so-called hypernephromata. One of us (Symmers) has had an opportunity to study an apparently identical tumor springing from the humerus of a woman, aged forty-eight years, who, while riding in an automobile, and from a trivial cause, sustained a fracture of the bone. Microscopic examination of tissue removed by curettement (Dr. George D. Stewart) revealed a tumor composed of colloid-containing

[1] Ann. d. Stadt. allg. Krankenh., München., 1910, xiv.

alveoli indistinguishable from those of the thyroid. There were definite indications of carcinomatous transformation. In addition the connective-tissue stroma supported innumerable large and small, thin-walled vascular channels packed by red blood cells and lined by a single layer of flattened endothelium. The question naturally arose as to whether the tumor represented carcinomatous metamorphosis of an aberrant thyroid in the humerus or a metas-



A, capillary distended by red blood cells and showing a circumferential layer of proliferating endothelium. At one end is a small subsidiary vascular channel lying in the endothelial layer; *B*, capillary vessel showing the presence of multiple subsidiary vascular channels; *C*, smaller vessels with their lumina almost completely occluded by proliferating endothelium; *D*, vessels distended by proliferating endothelial cells with only partial preservation of the lumen, which is occupied by red blood corpucles; *E*, spicules of bone lying in a moderately cellular fibrillar connective tissue. (Drawn with Edinger's apparatus.)

tasis from a primary adenocarcinoma of the thyroid gland itself. Nearly three years have elapsed and the patient is perfectly well.

Nauwerck[2] has described a so-called hyperplastic capillary angioma of the upper end of the femur. The tumor was composed of alveoli lined by cuboidal epithelial cells surrounding homogeneous plugs of colloid. In the supporting connective tissue were numbers

[2] Virchows Archiv, cxi, p. 211.

of capillary vessels. From the histological description of the growth as well as from the illustration which accompanies Nauwerck's article it is obvious that he was dealing with a vascularized thyroid rest of the same type as that encountered in the humerus by both Zetkin and Symmers.

The symptomatology of the condition which we have described above bears a close resemblance to that of the multiple myelomata—the occurrence of multiple primary tumors of the bones, particularly those with red marrow, including the skull, vertebræ, ischium, sternum, and ribs; excruciating pain and exquisite tenderness referable to the distribution of the osseous growths; apparent absence of visceral metastasis; regional infiltration of tissues following direct extension from the bone; spontaneous fracture; emaciation and anemia—all are symptoms highly suggestive of the myelomata. The resemblance is not vitiated by the absence of Bence-Jones protein in the urine, for not all cases of myelomata are attended by albumosuria and, moreover, the Bence-Jones protein has been demonstrated in the urine in lesions of the bony system other than myelomatosis.

Histologically the myeloma is a tumor springing from certain cytoblastic constituents of the bone marrow, and is oftenest composed of elements of the type of premyelocytes or of plasma cells. The tumor we have under consideration, however, presents totally different microscopic features in that it commences with overproduction of bloodvessels of the capillary variety and, as a result of continued proliferation of the lining endothelium, brings about distension of the vessel lumen and eventuates in its partial or complete occlusion by tumor cells. At the same time the tumor displays a remarkable tendency to produce subsidiary vascular channels within the lumen of the parent capillary.

THE DISTRIBUTION OF TETANUS TOXIN IN THE BODY.

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It has been a matter of common experience ever since the laboratory study of tetanus began that when one injects a sufficient quantity of tetanus toxin into the muscles of the hindleg of a laboratory animal—*e. g.*, guinea-pig or rat—that after a varying period of incubation the injected leg will become stiff and outstretched. Then, generally, the toxin affects in succession the other muscles of the body, first those of the hindleg on the opposite

side, next those of the back, and finally of the neck, thorax, and head. By this time convulsive seizures of increasing severity and with decreasing intervals have appeared, and at last, with asphyxia or exhaustion, death ends the scene. The convulsions are usually spontaneous, but may also be produced by sensory irritation, such as stroking, pinching, or a sudden noise. The inoculated limb, as a rule, remains stiff and outstretched until the moment of death, when it and the remaining muscles of the body become suddenly relaxed and softened, only to stiffen again after the rapid onset of *rigor mortis*.

If the toxin should be injected into other portions of the animal's body—*e. g.*, pleural cavity—instead of into the hindleg the gradual progression of the symptoms would not be so manifest and local or ascending tetanus[1] would appear. Either the muscles of the head and neck would be first attacked and then the remaining muscles in more or less regular succession, so-called tetanus descendens, or the order of the attack would be first local and then general without reference to the contiguity of the muscle groups or nerve centres, so-called mixed or general tetanus. Most of the laboratory animals, by inoculation into the muscles of an extremity, will exhibit local tetanus or tetanus ascendens. Tetanus in man or horses, on the contrary, is more apt to assume the form of tetanus descendens or general tetanus. No matter what may be the order of development, however, the symptoms are always so definitely similar and the clinical picture, as a whole, so unvarying that no argument is necessary to convince one of the specificity of the reaction.

That in natural infections by the tetanus bacillus this organism multiplies locally and elaborates a soluble toxin, which spreads throughout the body, is generally admitted; that the injection of an artificially prepared tetanus toxin into an animal's body in every way corresponds, in the principles governing its action, to the effect of a natural infection, hardly anyone will deny. But as to how this toxin spreads in the system, as to exactly what portions of the body are primarily attacked, and how this process is brought about, are questions which have led to long series of experiments, endless discussion, and many varied and opposing theories. It is not purposed here to discuss in detail all of the opinions which have been offered. For the present it will suffice to mention the more salient features of three important theories and discuss more extensively those which have a direct hearing on my own work and conclusions.

Among the former is the earlier work of Vaillard and Vincent, in which they expressed the belief that local tetanus was due to the direct action of tetanus toxin solely on the muscles themselves. Zupnik later developed and elaborated this assumption. He found

[1] For the accurate classification of these various types of tetanus (ascendens, descendens, and mixed) we are indebted to Zupnik.

that when he injected tetanus toxin into the subcutaneous tissues or into the nerve of an animal's foot at a point where the toxin could not come into contact with muscles the animals were affected by tetanus descendens and not localized tetanus. This latter form did not appear unless the toxin came into close association with muscular tissue, and when this took place those particular muscles were attacked by enduring spasmodic contractures which persisted for a long time and were not released by general anesthesia, curare, or cutting of the corresponding nerve trunks of the muscles. Zupnik attempted also to enervate completely the muscles of an extremity, and, by the injection of tetanus toxin into these muscles, he nevertheless obtained local tetanic spasms. He, therefore, concluded that the muscular phenomena of tetanus arose from direct intoxication of these muscles by the tetanus toxin.

This latter experiment of Zupnik's has been repeated, among others, by Sawamura and Permin, who were both able to show that when an animal's leg has been absolutely separated from all nerve connection with the spinal cord the muscles of that leg will always remain flaccid no matter whether the tetanus toxin be injected into these muscles or into some other part of the body. They believed that, due to faulty or incomplete enervation, Zupnik was able to obtain muscular spasms in the extremity so treated, because these muscles still retained some intact nerve fibers connecting them with the spinal cord. The other portion of Zupnik's evidence, namely, the enduring muscular contraction, requires more detailed consideration. As shown by experiment 8, when an animal dies from acute tetanus, following local injection of tetanus toxin, at the moment of death all the muscles of the body become soft, relaxed, and free from any stiffness or spasm.

Experiment 8.—Guinea-pig No. 3. Weight, 400 gms.

Jan. 29, 1915,	2.30 P.M.	Tetanus toxin,[2] 0.1 c.c. intraperitoneal.
Feb. 1, 1915,	8.00 A.M.	Right leg slightly stiff and extended.
Feb. 2, 1915,	8.00 A.M.	Right leg completely stiff. Beginning stiffness opposite leg.
Feb. 3, 1915,	9.00 A.M.	Rear portion of body entirely stiff and rigid. Spasms in muscles of back and neck.
	12.00 M.	All muscles of body except front legs affected. Respiration rapid.
	5.00 P.M.	Death (five days two and one-half hours). At moment of death entire body including hindquarters soft and freely movable.
	5.05 P.M.	Postmortem rigor, rapidly involving entire body.

[2] For the tetanus toxin and antitoxin used in these experiments, I am indebted to the kindness of the Hoechst Farbwerke, Hoeschst, a. M.

This observation has been repeated many times in mice, rabbits, and rats as well as in guinea-pigs. That the same relaxing effect may follow the administration of certain drugs in the acute stages of tetanus is seen in experiment 94, a portion of whose protocol is given below.

Experiment No. 94.—Rabbit No. 5. Weight, 3000 gms.

Mar. 24, 1915,	10.00 A.M.	Tetanus toxin, 0.5 c.c. (right hindleg).
Mar. 25, 1915,	10.00 A.M.	No symptoms.
Mar. 26, 1915,	8.45 A.M.	Slight stiffness in right hindleg.
Mar. 26, 1915,	9.40 A.M.	$MgSO_4$ (25 per cent. sol.), 7 c.c. subcutaneous.
	10.10 A.M.	Stiffness entirely disappeared.
	6.00 P.M.	Right leg again stiff. $MgSO_4$ (25 per cent. sol.), 8 c.c. subcutaneous.
	6.30 P.M.	All stiffness disappeared.

This experience was repeated a number of times with this rabbit and with other animals, and demonstrated that under the influence of appropriate narcotics all local spasms in acute tetanus may be temporarily removed. The same fact has been shown many times by others in various ways, *e. g.*, by cutting the motor nerves, by ether or chloroform anesthesia, or by injections of cocain or curare, and leaves no doubt that the primary action of tetanus toxin is not on the muscles but is on the spinal cord.

Certain facts, however, which have been observed by almost every laboratory worker on tetanus and which formed a part of the evidence advanced by Zupnik in favor of his theory, remain to be explained. When one produces a local spasmodic contraction in an animal's muscles by injection of tetanus toxin and the animal lives long enough—*i.e.*, does not die with acute tetanus—this spasmodic contraction may become more or less permanent. The following protocol is an example of this frequently observed phenomenon:

Experiment 21.—Guinea-pig No. 17. Weight, 540 gms.

Feb. 10, 1915,	12.15 P.M.	Hoechst antitoxin, 1 c.c. (5.2 units[3]) intraperitoneal.
	2.15 P.M.	Tetanus toxin, 0.3 c.c. in muscle of right hindleg.
Feb. 11, 1915.		Right hindleg extended and stiff. Animal otherwise normal.
Feb. 12, 1915.		Stiffness of right leg more pronounced.
Feb. 13, 1915.		Entire right hindquarter stiff and board-like. No other muscles affected.
Feb. 22, 1915.		Leg atrophied. Foot swollen. Animal runs and eats.

[3] German standard.

Mar. 1, 1915.	Weight, 470 gms. Appears thin. Otherwise the same.
Mar. 18, 1915.	Leg movable in foot portion. Swelling reduced. Weight, 500 gms.
April 23, 1915.	Leg movable in all portions. Slight stiffness at hip. Weight, 600 gms. (seventy-two days).

This same condition has also been repeatedly observed in rabbits and rats as well as in guinea-pigs. As has been shown by Goldscheider, Zupnik, Meyer and Ransom, Permin, and others, this sort of spasm does not disappear when the nerves are cut, or when narcotics or magnesium sulphate are given, or even after death. It is a long-enduring and almost inexhaustible stiffness which resists all attempts at passive motion, shows evidences of vascular and trophic alteration (atrophy and edema), and only after weeks and even months does it begin gradually to disappear. If the animal dies or is killed the changes found both grossly and microscopically are only those which might result from long and continuous non-use. Ribbert examined for Meyer and Ransom the spinal cord of a cat which had lived for five months with an unchanged tonic spasm of both hindlegs. He found that most of the ganglion cells of the anterior horns at this level showed degenerative changes. However, it appears probable that such changes are purely secondary, not representing in any way the primary action of the tetanus toxin on either the spinal cord or muscles. Just what combination of chemical changes must occur in order to convert a temporary and easily relaxable muscle spasm into an enduring one is not entirely clear. Gumprecht declared, "Dieser Starre der Muskeln ist nichts anderes als ein hochgradiges Ermuduengs-phaenomen, wie es den Physiologen vom electrischen Tetanus laengst bekannt ist." Meyer and Ransom suggest that such contractions represent a disturbance of the "muscle tonus" centres, which in their inexhaustibility and independence from volition are probably distinct from the motor centres. At any rate it becomes evident that the phenomenon cannot serve as proof for Zupnik's assertion.

The second of the three theories was advanced by Pochhammer who proposed to explain all local phenomena occurring in tetanus by the action of the toxin on the myelin sheaths of the peripheral nerves. According to him the tetanus toxin so alters the myelin that the normal insulation of the nerves is interrupted and "short circuits" may take place, especially in those nerve trunks which contain a mixture of sensory and motor fibers, whereby sensory stimuli pass directly across between the nerve bundles instead of being conducted along the normal reflex arc to the spinal cord. As a partial proof of this hypothesis he treated nerve trunks with ether, thus dissolving the lipoids in the myelin sheaths and producing an artificial "short circuit" which he asserted simulated that con-

dition which occurs in tetanus. This latter experiment was repeated by Permin, who admits that when the nerves are so treated a stiffness of the corresponding limb results; but he concludes that this stiffness is not at all similar to that which is found in tetanus. Sawamura further calls attention to the fact that the direct injection of toxin into the substance of the spinal cord or brain will produce a fatal tetanus. Here a "short circuit" of the peripheral nerves can hardly enter into the question. Moreover, if the tetanus toxin has its primary and sole effect on the peripheral nerves, it becomes difficult to explain, not only the non-neutralizing actions of these nerves when mixed with toxin, as shown by Meyer and Ransom, but also the neutralizing action of the brain-and-cord-toxin mixtures, as demonstrated by Wassermann and Takaki. Not only has Pochhammer's theory received no substantial support from other workers, but it does not explain satisfactorily the various phenomena arising as the result of the inoculation of tetanus toxin.

The third theory received its chief support from Autokratow as well as Courmont and Doyon, who believed that the local spasm resulted from an intoxication of the peripheral sensory nerves alone, so that the supposedly more or less normal motor ganglion cells received intensified sensory impulses and reacted in a correspondingly intensified manner. They based their theory in large part upon the results of the well-known experiment (performed among others also by Goldscheider and Permin) in which, by cutting the posterior (sensory) lumbar nerve roots between the spinal ganglion and the cord, all tetanic spasms in the hindleg of an animal, in consequence of the injection of tetanus toxin, are at once released, if they have been present before the operation, or do not appear in this leg at all. In short, cutting the posterior nerve roots prevents or removes tetanus spasms in the muscles which are supplied by those nerves.

Other workers have endeavored in various ways to show the relation which the sensory nerves and centres bear to the general phenomena of tetanus. Sawamura cut as many as possible of the sensory nerves of the skin of a rabbit's hindleg, thereby producing complete anesthesia, and then injected tetanus toxin into the muscles of that leg. While tetanus symptoms finally appeared in the injected extremity, they were slower in developing and less severe than those caused by the same amount of toxin in an unoperated animal. Meyer and Ransom, on the other hand, injected tetanus toxin into purely sensory nerves such as the nervus infraorbitalis and saw not only an unusually prolonged incubation but also a marked diminution in the severity of the reaction. By still another and more striking experiment they were able to show that motor phenomena alone need not play the major role in the symptomatology of tetanus. After carefully exposing the spinal cord in the lumbar region they uncovered the posterior roots and injected

tetanus toxin into one of these at a point between the lateral ganglion and the spinal cord. The animal developed a peculiar "sensory" type of tetanus, which they called "tetanus dolorosus" and which was characterized by the presence of a marked localized sensitiveness (Schmerzerregbarkeit), which was so extraordinarily pronounced that the slightest contact, even a light blowing on the skin of the affected area, led to a violent, apparently unbearable spasm of pain. These attacks also occurred in the form of paroxysms, interrupted by periods of comparative quiet. Owing to the fact that during these attacks the animal would bite at the affected area and make every effort to alleviate the acute pain, Meyer and Ransom concluded that the reaction represented "brain reflexes, *i. e.*, coördinated defensive movements (Abwehrbewegung)." Motor spasms or the usual muscular phenomena of tetanus were absent, the animal finally succumbing apparently only to exhaustion.

It thus appears clear that the sensory portion of the spinal cord and brain play some role in the production and maintenance of the typical spasms and convulsions of tetanus. One has only to observe closely the extreme sensitiveness to sensory stimuli which is exhibited by most tetanus patients to be convinced of the general application of this statement. To what extent, however, in the usual forms of tetanus there is a direct intoxication of the sensory nerve centres is by no means clear, and certainly it does not seem to be true that under ordinary circumstances the sensory nerves and those alone are affected. Referring again to the fundamental experiment in which is shown the effect on tetanus produced by section of the posterior nerve roots, may be mentioned the work on frogs by Hering, who cut the posterior roots during strychnin poisoning. So long as the motor neurons remained thereby isolated the animal showed no "strychnin convulsions," but on irritation of the central stump the state of increased excitability of the motor segment was at once manifest and typical tetanic spasms ensued. As strychnin admittedly affects the anterior horn cells of the spinal cord, this experiment would tend to show that also in tetanus the sensory fibers in the main merely serve to convey the stimuli necessary to set in operation the motor apparatus—in other words it demonstrates the physiological maxim that the motor ganglion cells do not act purely automatically.

According to Brunner, Goldscheider, Gumprecht, Marie and Morax, Stintzing, Meyer and Ransom, and Sawamura, the spasmodic contraction of the muscles seen in local tetanus results from the action of tetanus toxin on the anterior horn ganglion cells of that portion of the spinal cord governing the muscles of the affected extremity. In their opinion the toxin passes to these ganglion cells by way of the motor nerves, a theory with which most of the writers on experimental tetanus are today in full accord.

Meyer and Ransom, Marie and Morax, and Sawamura contend that this conduction of the toxin must take place along the axis-cylinders, or, as Meyer and Ransom say, "Das Gift muss also im Fibrillenplasma stroemen."

As proof of this contention, Marie and Morax injected tetanus toxin into the hindleg of a guinea-pig and after a definite lapse of time, by killing the animal, cutting out the sciatic nerves and inserting pieces of these under the skin of mice, were able to demonstrate the presence of toxin in the nerves of both legs, particularly in those of the inoculated leg. The blood of these guinea-pigs was also found toxic but not the muscles of the inoculated limb. This diffusion of toxin to the nerves, if they were normal, occurred within one and a half hours. If, however, they had been previously sectioned, twenty-four hours were necessary before any amount of toxin could be demonstrated in the peripheral or distal portion, while if one allowed six or more days to elapse, or until degenerative processes had had time to occur, no toxin at all could be shown to be present. The proximal or central portion of these cut nerves did not contain virus. Even when toxin was injected into other areas, such as the vitreous humor of the eye or the testicle, its presence could still be detected later in the sciatic nerves. If a nerve which had already absorbed toxin was cut this toxin rapidly disappeared from the central portion, and when toxin was injected into the lumbar swelling of the spinal cord it spread upward in the cord but not to the peripheral nerves. From these and similar experiments the authors concluded that the toxin was absorbed by the muscle nerve endings and passed centripetally to the spinal cord by way of the axis-cylinders and not either by nerve sheaths or by lymph channels.

This demonstration of tetanus toxin in the nerve trunks of peripheral nerves following intramuscular injections has been repeated and confirmed many times, among others by Pochhammer, Meyer and Ransom, Sawamura, and Permin. Also the retardation or even complete interruption in toxin absorption, which follows cutting the nerves of an injected limb, has been fully proved. For Meyer and Ransom these facts were sufficient grounds for postulating the condition of tetanus toxin in the axis-cylinders.

However, exception to this current view must be taken so long as it is not better supported. An important theoretical consideration in this connection must be mentioned. While, according to this theory, the toxin is conducted to the spinal cord and throughout the cord itself in the fibrillar structures of the axis-cylinders, both its chemical union and its toxic effect are supposed to take place in the protoplasm of the ganglion cells. This combined assumption is perhaps admissible, but, up to the present time, has not been demonstrated to be true for any other toxic substance. If the axis-cylinders really possess such a marked affinity for toxin

that they can conduct this from the peripheral portions throughout the entire nervous system, the ultimate union with the protoplasm of the ganglion cells appears rather difficult to explain. Meyer and Ransom found that when normal sciatic nerves were cut and brought into contact with tetanus toxin *in vitro* they exhibited no particular power to fix the toxin. From this they concluded that the affinity between tetanus toxin and nerve substance was not the same kind as that which had been demonstrated by Wassermann and Takaki to exist between this toxin and brain or cord substance. But if the axis-cylinder theory holds true there must be some sort of affinity exerted by these structures for the toxin. Can this be denominated as a hitherto unknown "affinity to travel?" The axis-cylinders are an integral part of the ganglion cells, and if the protoplasm of these cells can remove the toxin from their own processes because of a special chemical affinity for it, it is difficult to understand why these cells cannot also take up toxin from the surrounding lymph.

In short, that tetanus toxin travels in the fibrillar substance of a nerve structure without being in any demonstrable manner bound by this substance, and that it is readily delivered to another element of these same structures (ganglion cell body) to form a firm chemical union, rather than that it travels in those paths natural and adapted for the passage to the cells of all substances in a fluid state—namely, in the lymph channels—from a purely theoretical stand-point does not appear to be sound doctrine. On the contrary, it is much easier to explain not only the natural manner of distribution of fluids to the tissues of the body, but also the facts in regard to the distribution of tetanus toxin to the central nervous system by supposing that this takes place by means of the lymph.

Apart from such theoretical considerations, one of the main arguments for toxin conduction by the axis-cylinders—namely, the delay or complete failure in toxin absorption after cutting the nerves—may as reasonably serve to support the conduction-by-lymph theory when attention is directed to the fact that, after cutting the nerves, the myelin sheaths of the peripheral fibers undergo degeneration and their disintegration products can be demonstrated histologically as more or less completely blocking the lymph channels. If it is true, as Gumprecht also asserted, that toxin absorption takes place through the lymph channels, then any paralysis of an extremity must diminish the rate of toxin absorption because of the failure of muscular activity. Also the longer the time which elapses after cutting the nerves, so much more complete will be the stoppage of the lymph channels until any further absoprtion becomes impossible. To the importance of these factors, Aschoff (through Rosenbach) has already called attention in connection with the absorption of adrenalin.

Permin removed the perineurium from a sciatic nerve and found

that, after injection into its peripheral portion, toxin affected the body fully as rapidly as in a normal control animal. But in concluding from this experiment that the toxin must travel in the nerve substance itself and not in the lymph passages he overlooked the fact that countless other lymph channels, aside from those in the perineurium, course freely in the nerve trunks themselves.

Further evidence, however, remains to be explained. Meyer and Ransom, whose really brilliant work on experimental tetanus has done so much to clear up many mooted points in our knowledge of this disease, and who have been very active supporters of the "axis-cylinder conduction theory," carried out the following experiment: A rabbit was treated with tetanus toxin and highly immunized until a test of its blood showed that 1 c.c. held one-tenth antitoxin unit of 4,000,000 −Ms.[4] A large dose of tetanus toxin (5000 +Ms.) was injected subcutaneously without effect. Then in the left sciatic nerve a very small second dose of toxin (200 +Ms.) was injected and the animal on the following day showed severe tetanic spasms, particularly in the muscles of the left leg. A test of the blood removed at this time showed the antitoxin content unchanged. Tests of the cerebrospinal fluid and of the nerve lymph also showed the presence of antitoxin but "much less than the blood." Permin, who repeated and confirmed these results, also proved that a similar reaction can be obtained in an even simpler manner by injecting the antitoxin into the blood stream of a rabbit or dog and shortly after by an injection of toxin into the muscles of the hindleg, whereby a local tetanus ensues which is confined to the muscles of the inoculated leg. In my experiments on rats and guinea-pigs with the prophylactic application of antitoxin I have encountered the same phenomenon, namely, after the injection of concentrated toxin into the muscles of a passively immunized animal, local tetanus of the muscles of the injected leg would appear. Often this stiffness also affected the back muscles of the corresponding hindquarter, but, unless the dose of toxin was overwhelmingly large, this condition did not spread any further and did not endanger the life of the animal.

The possibility, then, must be admitted that tetanus toxin may travel along a nerve trunk to the spinal cord in the body of an actively or passively highly immunized animal, from which fact Meyer and Ransom concluded that the toxin in its passage along the nerves is not conducted in the lymph but, as quoted above,

[4] The antitetanus serum unit, established by Behring and used to measure the potency of German serums, represents that amount which will protect one gram of mouse weight against 40,000,000 lethal doses of toxin. A unit lethal dose of toxin for 1 gram of mouse weight is denoted by the sign +Ms. The designation −Ms. refers to the amount of serum necessary to save 1 gram of mouse weight from the fatal effect of a unit lethal dose of toxin (1 +Ms.). Hence 1 A.E. (antitoxin einheiten) or unit represents 40,000,000 −Ms.

"Das Gift muss also im Fibrillenplasma stroemen." Permin from the same fact drew a similar conclusion, namely, that the experiment demonstrates that the nerve substance itself must be regarded as the conducting medium. This conclusion does not seem to be fully justified, and I believe that the facts can be better explained by the "lymph channel theory." Following injections of toxin, tetanic symptoms are produced simply because the tetanus toxin is concentrated enough to more than neutralize the antitoxin present and thereby can pass through the lymph channels to varying distances up the spinal cord before it is rendered harmless by the circulating antitoxin or is fixed by the nervous tissue.

When Meyer and Ransom and also Sawamura injected tetanus antitoxin into a nerve trunk they found that this particular nerve and its corresponding nerve segment were fully protected from the action of the following injection of tetanus toxin, no matter whether this toxin was injected directly into the same nerve or into some neutral area. In other words, they provided antitoxin in sufficient local concentration to neutralize an equally or less locally concentrated toxin.

Ransom has shown that in whatever manner either tetanus toxin or antitoxin may be injected into the body, they both shortly appear in the blood stream and thence in the lymph. The antitoxin apparently remains in the blood and the lymph until its final disappearance from the body, while the toxin is largely taken up by the nerves, conveyed to the cord and brain, and there fixed in the protoplasm of the ganglion cells. However, it seems well established that the lymph channels of the body, apart from the site of injection, never contain antitoxin in very concentrated amounts and this appears to be equally true of the lymph spaces of the central nervous system. Indeed, Meyer and Ransom assert that antitoxin does not enter the central nervous system by way of the blood and lymph streams, an opinion which perhaps expresses too strongly the *paucity of concentrated antitoxin* in that part of the body for later in the same paper (p. 413), in discussing the researches of Roux and Borrel, who were able to produce tetanus in highly passively and also actively immunized dogs by injections of toxin into the cerebral substance, Meyer and Ransom suggested that "the toxin concentrated at the site of injection could not be at once neutralized by the antitoxin which was certainly present in the centres although in low concentration, and consequently, enough time elapsed in which to poison the nerve cells before sufficient additional antitoxin-laden blood appeared; we have to deal, then, with a regional difference of concentration." This condition of affairs also maintains when concentrated toxin is injected in or near a nerve trunk, and the facts brought forth in this connection cannot serve as arguments in favor of the conduction of tetanus toxin along the axis-cylinders.

On the contrary, the evidence so far presented by the numerous workers is distinctly in favor of the theory which designates the lymph channels as the natural medium of exchange for fluids between the different portions of the body, including the central nervous system.

The chief supporters of this latter view have been Gumprecht and Stintzing, the last named having reported the presence of tatanus toxin in the cerebrospinal fluid of two human cases of tetanus. This finding has not been sufficiently confirmed either in cases in men[5] or by animal experimentation (Ransom). I have tested on white mice the cerebrospinal fluid from two severe fatal cases of tetanus and was unable to prove the presence of tetanus toxin. Gumprecht's conclusions, on the other hand, were based on purely experimental grounds. He injected tetanus toxin into the subdural space of the lumbar cord and found that tetanus appeared first in that extremity corresponding to the side on which the injection was made. He called attention to the injection experiments of Key and Retzius, who, by means of Berlin blue and gelatin (Richardson's blue), found that not only are the peripheral nerves and spinal cord full of intercommunicating lymph channels, so rich that even each individual fiber is surrounded, but also that everywhere along the cord are free communications with the subarachnoidal lymph spaces, which spaces in turn freely open into the lymph channels of the perineurium. Therefore Gumprecht stated that "after injection into the hindleg the toxin readily ascends in the numerous lymph spaces of the nerves and on reaching the spinal cord is diffused both up and down (in the cord)."

I have repeated in part Key and Retizius's injection experiments, and have found that by injecting the sciatic nerve a short distance below the spinal ganglion with Richardson's blue the fluid passes freely through the ganglion toward the cord along the motor roots. The lymph channels of the sensory roots are either not injected at all or injected with difficulty by this means. Neither does there appear to be such free communication between the endoneural spaces and the subarachnoid spaces as Key and Retizius indicated, for when the injecting needle is kept in the central portions of the nerves the fluid mass remains within the nerve sheaths and does not invade the arachnoid unless rupture from undue force occurs. The point is of some importance, as it not only explains why tetanus toxin under ordinary circumstances does not pass into the cerebrospinal fluid, and thus why Stintzing's observations have not been fully confirmed, but also it perhaps gives a hint as to why the usual type of tetanus is a motor tetanus and not "tetanus dolorosus," as obtained by Meyer and Ransom when they injected

[5] While most workers report uniformly negative results it should be noted that Permin claims to have demonstrated tetanus toxin in the cerebrospinal fluid of five human cases.

toxin into the posterior roots. In other words, the toxin by following the lymph channels passes first to the motor side of the cord.

Meyer and Ransom repeated Gumprecht's experiment of injecting tetanus toxin into the subdural spaces and confirmed his results. However, while Gumprecht believed that the toxin passed directly by means of the perivascular spaces to that portion of the spinal cord with which it first came into contact, on the other hand, Meyer and Ransom concluded that it was first absorbed into the blood stream, taken up by the peripheral nerves, and thus conveyed in the usual manner to the spinal cord, where that part which had been injured by the injection, a *locus minoris resistentiae*, would be the first affected. This hypothetic injury, they believed, was impossible to avoid.

It is necessary to note here an experiment of Permin, whose views, as stated, are in full accord with those of Meyer and Ransom. After injecting tetanus toxin into the muscles of the hindlegs of rabbits, and at the same time antitoxin into the blood stream (to prevent general tetanus), he injected antitoxin intraspinally at varying intervals of time. Such injections had to be made within at least four hours after the injection of the toxin in order to prevent the outbreak of a local tetanus. Permin does not explain how this result was accomplished, but it is reasonable to suppose that the antitoxin passes into the lymph channels of the nerve roots and there neutralizes the ascending toxin which must also be in the nerve lymph. From this experiment he rightly concludes that the conduction of toxin in the nerves must proceed with extraordinary rapidity (p. 24), a fact which is well explained by the rapid movement of lymph in the nerve sheaths. Pochhammer, in support of his theory after injecting tetanus toxin into the leg muscles of rabbits, killed the animals, cut out the corresponding sciatic nerves, and, dividing them into three parts, placed each piece under the skin of mice. He found that the peripheral portions of these nerves always held more toxin than the central portions. Sawamura fully confirmed these observations, which also agree with Meyer and Ransom's experiment, in which they found that after cutting a nerve holding toxin this toxin rapidly disappeared from the central or proximal end. While the conclusions derived from these various experiments were different and even contradictory, the results seem to be in full accord with the theory of tetanus toxin conduction by nerve lymph channels. This conduction naturally is slower in the finely divided distal nerve branches, but as the larger nerve trunks are reached and the lymph finds wider spaces through which to travel, the speed is accelerated and not only does the toxin spread faster but it is more diluted by the inflowing lymph currents and can thus more readily be neutralized by the less concentrated antitoxin. It is not possible to explain all these facts by the axis-cylinder conduction theory.

One further expriement was suggested by Professor Aschoff which might throw more light on the subject. This experiment is based

upon the theory that if tetanus toxin is conveyed by the axis-cylinders of the peripheral nerves to the spinal cord, it must also pass up the cord by the same means, while if conveyed to the cord by the lymph channels it must likewise spread by means of the lymph channels. But the spreading of toxin by means of the lymph channels can be prevented by a previous administration of antitoxin, which same, on the other hand, should not prevent the passage of toxin along the axis-cylinders. Hence, if toxin be injected into the lower end of the spinal-cord substance of a passively immunized animal, the manner in which the animal reacts should furnish decisive evidence in favor of one or the other contention. The protocols of these experiments are as follows:

Guinea-pig No. 38. Weight, 350 gms.

April 20, 1915. 1 c.c. tetanus antitoxin, subcutaneous. Twenty-four hours later, under ether anesthesia, the lower portion of the back was prepared for a surgical operation. Through a 5 cm. longitudinal skin incision the fascia and muscles were cut away and by sharp-pointed scissors the spinous processes and posterior portions of the lowest lumbar and upper sacral vertebræ removed, thus exposing the terminal portion of the sacral and lower lumbar cord. Into this exposed cord by means of a fine needle, inserted as far up as possible, 0.1 c.c. of tetanus toxin slowly injected.[6] The needle left in place a few minutes and then slowly removed. Muscles and fascia then carefully brought together by sutures, the skin sewed and the wound covered with an iodoform-collodion dressing. One-half hour later the guinea-pig runs about and is apparently normal in all its movements. On following day there was some distention of bladder by retained urine, which is relieved by gentle pressure on lower abdomen. No tetanic symptoms. Animal eats and runs about in normal manner. Forty-eight hours later the condition was the same. Bladder paralysis has disappeared. Ninety-six hours later there were no symptoms of tetanus or infection of wound.

Control. Rat No. 59. Weight, about 150 gms. Tetanus toxin, 0.003 c.c. in left hindleg. Forty-eight hours later there was marked local tetanus in the left hindleg.

[6] As can be seen by the control experiment this dose was about fourteen times that which would produce tetanus symptoms in the same weight of rat body.

Guinea-pig No. 25.

Mar. 26, 1915. Antitoxin, 0.4 in left hindleg. Five hours later, antitoxin, 0.1 c.c. again in left hindleg.

Mar. 27, 1915. Spinal column and outer end of spinal canal exposed through opening in dura. Toxin, 0.02 c.c. injected into canal.

Mar. 28, 1915. General condition good. Runs about and eats. Bladder and rectum paralyzed.

Mar. 29, 1915. Condition the same. No signs of tetanus.

Mar. 31, 1915. Weaker. Animal killed by ether. No evidence of tetanus. Autopsy: bladder markedly distended. Kidneys show hydronephrosis. Wound clean.

Guinea-pig No. 39. Weight, 500 gms; pregnant.

April 20, 1915. Tetanus antitoxin, 1 c.c., subcutaneous.

April 27, 1915. Injection repeated.

April 28, 1915. The same operation as in No. 38 only slightly higher up and 0.15 c.c. toxin injected into the spinal cord. Animal recovered from operation. Bladder paralyzed. (Control rat died at end of five days). Animal became weaker and without showing the slightest symptom of tetanus was killed after six days. Autopsy showed dead fœti. Wound clean.

Guinea-pig No. 41.

May 6, 1915, 8.00 A.M. Tetanus antitoxin, 1 c.c. in left hindleg.

10.30 A.M. Same operation on spinal column as described above and 0.2 c.c. tetanus toxin injected into the spinal cord.

11.00 A.M. Animal recovered from operation. Eats and runs about.

6.00 P.M. Slight stiffness in hindleg.

May 7, 1915, 10.00 A.M. No further evidences of tetanus. Twenty-six hours after operation animal died suddenly.

12.50 P.M. Autopsy: hemorrhages and pneumonia in both lungs. Spinal cord swollen and moist.

Guinea-pig No. 42.

May 10, 1915. 1 c.c. tetanus antitoxin, subcutaneous. After twenty-four hours, operation as described above and injection of 0.2 c.c. tetanus toxin. No trace of paralysis or tetanus at any time. Control rat dead from typical tetanus after two and one-half days.

These experiments demonstrate that by the injection of tetanus toxin into the lower end of the spinal cord of a passively immunized

animal, this toxin, even in doses which were sufficient to provoke symptoms in control animals, neither produced any marked local effect nor advanced in the spinal cord toward the more sensitive centres of the medulla, in short, that it was not taken up by the axis-cylinders but was prevented by antitoxin from spreading along its natural and customary route, namely, the lymph channels. The experiment moreover confirms in another manner the observation already noted on the occurrence of local tetanus when toxin is injected into the sciatic nerve or into the muscles of an animal's hindleg. In the presence of antitoxin in the system, tetanus toxin, whether injected into the hindleg or into the lower end of the cord does not travel far in the cord, because manifestly as it become more diluted, the antitoxin which is present in the lymph spaces of the spinal cord as well as in the lymph channels of the nerves has an opportunity to neutralize fully the less concentrated toxin and thus protect the portion of the nervous system lying above. The efficiency of this protection is exactly in proportion to the concentration of the antitoxin as compared with that of the toxin.

The objection raised by Permin that if toxin is transported in the lymph spaces of the spinal cord it would be difficult to explain the marked local tetanus which occurs when the leg of an immunized animal has been injected with toxin, does not assume so much weight when we take into consideration the fact that the concentrated toxin passes to the cord by definite lymph channels which are more or less closed until they reach the widely spreading spaces of the cord itself.

I have developed this theme at some length, believing it to be not only of theoretical but also of more than ordinary practical importance. Prophylactic or therapeutic methods in the rational treatment of any disease must be based, as far as possible, upon our knowledge of the causes of this disease and the manner of operation of these causes in the body. Hence in tetanus: if we assume that the path of attack of the toxin in the central nervous system is the axis-cylinders of the cerebrospinal nerves, then our plans for both prevention and treatment should be considerably different from those which should be adopted, if we believed the toxin to be distributed to the ganglion cells by the lymph stream. Terminal nerve fibrils are abundant over especially the entire tegumentary and muscular portions of the body. If they possess for tetanus toxin a "conductive affinity," then, in spite of all we may hope to accomplish even by prophylaxis, without complete enervation of the local area where the toxin is elaborated, the absorption by these fibrils of toxin before it can possibly be neutralized and the subsequent intoxication of corresponding nerve centres cannot be prevented by any means which, at present, is at our command. Antitoxin, admittedly, does not travel in the

nerve fibrils but in the lymph channels, and hence the passage of toxin, on the basis of the above theory, cannot be interrupted.

However, it would appear more reasonable to assume that tetanus toxins, just as other poisons, pass throughout the body exclusively by the blood and lymph streams and, theoretically, may be neutralized by antitoxin and at any stage in this passage before the final and comparatively indissoluble union with the ganglion cells occurs. The practical difficulties associated with neutralizing, by injections of antitetanus serum, the toxin already in the nerve trunks, in cases of outbroken tetanus, have been discussed in a previous paper.[7] But assuming the lymph-conduction theory to be true, these problems, however practically insurmountable they may be at the present time, are still capable theoretically of solution, and no doubt in the future some method may be found for the immediate protection of threatened nerve cells and perhaps even the saving of those already attacked. At least the situation is by no means hopeless.

In this connection may be seen the rationality of Behring's early endeavors to obtain a highly potent antitetanus serum, a serum so concentrated that, diluted as it must be by all the tissue fluids of the body, when it comes into contact with toxin it shall possess enough "neutralizing mass" to meet and overcomes this toxin, before the vital centres can be affected.

REFERENCES.

1. Autokratow. Recherches expérimentales sur le mode de production des contractures, Arch. de méd. exp., 1892, I serie, tome iv, p. 700.

2. Brunner. Die bisherigen Resutate experimenteller Untersuchungen über die Art der Wirkung des Tetanusgiftes auf das Centralnervensystem, Deutsch. med. Wchnschr., 1894, Nr. 5, s. 100.

3. Courmont et Doyon. Marche des contractures dans le tétanos expérimental chez les solipèdes, Compt. rend. Soc. de biol., 1892, t. iv, p. 1003.

4. Goldscheider. Wie wirkt das Tetanusgift auf das Nervensystem? Ztschr. f. klin. Med., 1894, Bd. xxvi, s. 175.

5. Gumprecht. Versuche über die physiologischen Wirkungen des Tetanusgiftes in Organismus, Arch. f. d. ges. Physiol., 1895, Bd. lix, s. 105.

6. Gumprecht. Kritik der neuren Arbeiten über die physiologischen Wirkungen des Tetanusgiftes, Deutsch. med. Wchnschr., 1895, Nr. 42, s. 693.

7. Hering. Ueber die nach Durchschneidung der hinteren Würzeln auftretende Bewegungsloskeit des Ruckenmarksforsches, Pflüger's Arch. f. d. ges. Physiol., 1893, Bd. liv, s. 614.

8. Key und Retzius. Studien in der Anatomie des Nervensystem und des Bindgewebes, Stockholm, 1876.

9. Marie et Morax. Recherches sur l'absorption de la toxine tétanique, Ann. de l'Inst. Pasteur, 1902, t. xvi, p. 818; also 1903, p. 335.

10. Meyer und Ransom. Untersuchingen über den Tetanus, Arch. f. Path. u. Phar., 1903, Bd. xlix, s. 369.

11. Permin. Experimentelle und klinische Untersuchungen über die Pathogenese und Therapie des Starrkrampfes, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1912, Bd. xxvii, H. 1, s. 1.

[7] Robertson, The Therapeutic Applications of Antitetanus Serum, Am. Jour. Med. Sci., 1916, cli, 811.

12. Pochhammer. Experimentelle Untersuchungen über die Entstehung des Starrkrampfes und die Wirkung des Tetanus toxins im menschlichen und tierischen Organismus, Samml. klin. Vortr., 1909, s. 149–151, Leipzig.
13. Ransom. Die Verteilungen von Tetanusgift und Tetanusantitoxin im lebenden tierischen Koerper, Berl. klin. Wchnschr., 1901, Nr. 13 u. 14, s. 337 u. 373.
14. Rosenbach. Ueber Adrenalinwanderung im Nerven, Deutsch. med. Wchnschr., 1908, Nr. 28. Sitz. Naturf. Gesell. im Freiburg i. B.
15. Ribbert. In Meyer and Ransom, Arch. f. Path. u. Phar., 1903, Bd. xlix.
16. Roux et Borrel. Tétanos cérébral et immunité contre le tétanos, Ann. de l'Inst. Pasteur, 1898, Nr. 4, xii, 225.
17. Sawamura. Experimentelle Studien zur Pathogenese und Serumtherapie des Tetanus, Arb. a. d. Inst. z. Erforsch. d. Infectionskrankh. in Bern, 1909, H. 4.
18. Stintzing. Beitrag zur Lehre des Tetanus traumaticus inbesonders zur Spinalpunktion und Antitoxinbehandlung bei demselben, Mitt. a. d. Grenzgeb. f. Med. u. Chir., 1898, Bd. iii, H. 3 u. 4, s. 461.
19. Vaillard et Vincent. Contribution à l'etude du tétanos, Ann. de l'Inst. Pasteur, 1891, s. 2.
20. Zupnik. Ueber experimentellen Tetanus descendens, Deutsch. med. Wchnschr., 1900, Nr. 52, s. 837.
21. Zupnik. Ueber den Angriffspunkt des Tetanusgiftes, Wien. klin. Wchnschr., 1902, Nr. 4.

STUDIES ON A CASE OF IDIOPATHIC PURPURA HEMORRHAGICA.

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Purpura hemorrhagica is a condition that is characterized in its severer forms by hemorrhage from the mucous membranes, petechiæ or ecchymoses of the skin, a markedly reduced platelet count, a much prolonged bleeding time and non-retractile blood clot. A normal or somewhat delayed coagulation time occurs.

In its milder form there may be but ecchymoses following injury or excessive bleeding from some local cause; the other characteristics mentioned above, though present, are not so extreme. In this country, Duke[1] [2] especially has studied this condition.

This form of purpura, though often not clearly differentiated in the literature from other types of purpura and hemorrhagic disease, can be easily distinguished from them, because in these conditions there is no reduction of the platelet count.

Purpura hemorrhagica may occur as an idiopathic disease, though more frequently perhaps as a symptom complicating various diseases, especially aplastic anemia, leukemia, tuberculosis, nephritis, etc. A congenital idiopathic type exists.

Case Report. Various studies on a case of the idiopathic type which died in spite of eleven transfusions of blood are presented

[1] Arch. Int. Med., 1912, x, 445. [2] Jour. Am. Med. Assn., 1910, lv, 1185.

below. A summary of the case which entered the hospital February 16, 1915, is as follows:

Number 200344. Russian Jewess; unmarried; aged eighteen years. Lived in Massachusetts twelve years. Her only work has been studying at school. Her home in Salem is clean, well ventilated, and in a good locality.

Family History. Entirely negative. No known exposure to tuberculosis.

Past History. She has always been strong and well except for mumps, measles, and diphtheria, which diseases she had as a small child. Her habits and bodily functions have been normal. Three weeks before her illness began she moved to a new house, owing to the Salem fire. This caused no undue excitement. Except for this, nothing unusual has happened to her in the past two years.

Present Illness. In July, 1914, she first noticed a few small, pea-sized, well-defined red spots on her feet and ankles which turned darker in color. Later the spots sometimes appeared as larger red areas or areas of bruised flesh. Since July she has never been free of such spots on her body, some disappearing as others reappeared, being more evident some weeks than others.

By degrees the spots appeared higher and higher on her body, reaching her face about a month before entrance, never, however, being marked on the abdomen. No bleeding occurred from the mucous membranes until about a week before entrance, but in the past week blood has been more or less continually oozing from the gums. During the past three days there has been a dull pain in the left hip, and today in the right jaw. She considers her general health good. There have been no systemic symptoms except that her menstrual periods have become more painful with an excessive amount of flow. A period is now present.

Physical Examination. A well-developed and nourished girl appearing distinctly pale. Scattered all over the body, but least on the trunk are very many discrete, rarely confluent hemorrhagic macular areas 1 to 5 mm. in diameter, especially prominent over the tibiæ, which are somewhat tender to pressure. The scleræ of both eyes show several pin-point hemorrhagic spots. The mucous membranes of the mouth and tongue show numerous discrete hemorrhagic areas. There is a large hematoma in the soft palate. A few bleeding-points occur in the gums about the teeth. Excessive menstrual flow.

Roentgenological Examination (Dr. Holmes). Teeth and sinuses: "Question of pus about right lateral incisor. Small right frontal sinus. No pus." Tibiæ: "Slight cortical thickening, otherwise negative."

Except for the above the physical examination was entirely negative. The abnormal laboratory findings will be discussed below.

Summary of Clinical Notes. February 23. The purpuric spots have nearly all gone. Bleeding from vagina and gums stopped three days ago.

February 28. A fresh crop of spots have appeared over skin and mucosa of mouth. Bleeding recurs from gums and vagina.

March 5. Spots have been increasing over arms and legs, increased profuse bleeding from gums, slight increase from vagina. Positive guaiac test on stool.

March 8. First transfusion, 300 c.c. of blood. Bleeding not checked.

March 10. Guaiac test on stool negative. Spots on skin fading. Less bleeding from gums and vagina.

March 11. Second transfusion, 900 c.c. of blood.

March 12. No new skin lesions. Distinctly less bleeding. Pelvis full of clots. Temperature rising.

March 19. There has been no further bleeding from gums and no new skin lesions; bleeding from vagina, however, has been persistent, though not severe.

March 23. General abdominal pain; no spasm. Vomiting two to three times a day in past two days. Small amounts of blood in vomitus. In past four days increasing bleeding from gums and vagina.

March 24. Third transfusion, 900 c.c. of blood. Less bleeding tonight.

March 26. Slight bleeding from gums. Less from vagina since transfusion.

April 2. Increased vaginal bleeding, daily. Severe bleeding from gums recurs today, there having been none for four days. Small amount of blood in catheter specimen of urine. Very rare minute punctate hemorrhages in skin of arms and legs. Patient appears much sicker. Fourth transfusion, 1000 c.c. of blood.

April 6. The only bleeding since the last transfusion has been a slight amount from the vagina. Tonight, however, the gums began to bleed again. The vaginal bleeding doubled in amount.

April 12. Continued increasing bleeding from gums, with petechiæ on lips. Vaginal bleeding profuse. No skin lesions. Fifth transfusion, 900 c.c. of blood.

April 20. Vaginal examination negative except for clots in vagina.

April 29. Since the last transfusion she has felt better and there had been no bleeding of any sort except for very slight bleeding of gums on April 21, a very few small purpuric spots on April 24, and upon sitting up in a chair on April 27, numerous small petechiæ appeared on the lower legs.

May 3. In past three days slight bleeding from gums. Few small purpuric spots appear on back of neck and legs today. Vaginal bleeding commences again.

May 18. There has been continued and increasing bleeding from

gums and vagina. Blood appears in urine. Generalized purpuric skin lesions, distinctly fewer and smaller than on entrance, appeared May 11. A few small new spots have appeared each day since. Sixth transfusion, 900 c.c. of blood. Marked bleeding from wound.

May 23. Daily increasing amount of bleeding from gums and vagina with persistent hematuria. No new skin lesions. In general, appears sicker. Seventh transfusion, 900 c.c. of blood. In the evening following this transfusion the bleeding from the gums and kidneys stopped but persistent vaginal flow continued.

May 26. Hemorrhage into right retina. Few hemorrhagic spots in both scleræ. No bleeding from gums. Excessive bleeding from vagina. A little bleeding from kidneys.

May 27. Eighth transfusion, about 700 c.c. of blood.

May 29. Very little bleeding from any source. Patient transferred to surgical service, and Dr. Davis did a hysterectomy with double salpingoöphorectomy followed by the ninth transfusion of blood, 1100 c.c. The ovaries were cystic, containing hemorrhagic fluid. Dr. W. F. Whitney reports "hyperplastic endometritis."

June 1. Since operation, though gradually diminishing, there has been severe oozing from both abdominal and transfusion wounds, though dressings reinforced, they are repeatedly and frequently stained through. Very little bleeding from vagina. None from gums and no skin lesions.

June 3. Bleeding from gums recurs. Another retinal hemorrhage. Few petechiæ about lips. Dysuria with large amount of blood in catheter specimen of urine. No bleeding from operation wounds.

June 11. Continued persistent bleeding daily from kidneys and mucosa of mouth. Slight bleeding from vagina. Tenth transfusion, 1000 c.c. of blood.

June 15. Since last transfusion no bleeding from vagina. Though distinctly less, some from gums and kidneys. No skin lesions.

June 25. Her general condition is better, still there has continued daily hematuria which though perhaps diminishing is plentiful today. "Coagulen" 5 gm. subpectorally.

June 26. No hematuria.

June 28. Hematuria reappears.

June 30. Five grams of "coagulen" subpectorally.

July 3. There has been no further hematuria or bleeding. Eleventh transfusion, 800 c.c. of blood.

July 4. In the past two weeks there has been a distinct improvement. Patient discharged today.

During July the patient was not seen, but stated that at times, though she had slight bleeding from her gums, had seen no blood in her urine, and but occasionally a small purpuric spot on her skin. In early August she felt weaker, had perhaps some blood in her urine, and had bleeding from her gums. The patient was

last seen August 14, when she had numerous purpuric lesions scattered over her arms and legs and mucosæ, with bleeding from her gums but no hematuria. Death occurred about August 29. There was no autopsy. From the history given by the family it seems that she gradually grew weaker without any extensive bleeding, and that possibly death may have been caused by a cerebral hemorrhage.

Temperature, Pulse and Respiration. During the patient's stay in the hospital, the temperature usually fluctuated daily 1° or so.

From entrance, February 16, until March 1 the temperature remained between 99° and 98°. Between March 1 and March 16, between 99° and 101°. A temperature between 102° and 104° occurred during the next week, and from then until April 15 a temperature of between 101° and 102° and 99° was seen. In the next two and a half weeks, 98° to 99° then fluctuating between 98° and 100.5° until June 5. From June 5 to June 26 fluctuations of often 2° a day occurred between 100° and 103°. From then until discharge, July 4, a gradual drop to 98° to 99° occurred.

The pulse followed the temperature, being 80 to 90 in the first weeks with the temperature 98° to 99°, but tended, as the disease progressed, to reach a higher level of about 105 with the same temperature. With the temperature 99° to 101° the pulse was 100 to 120, often rising to 140 or even 150 when the temperature was above 101°.

The respirations averaged about 22, reaching 26 to 30 with the highest temperature.

Laboratory Examinations. *Urine:* The urine was examined frequently while the patient was in the hospital and was negative except for the findings given below. There was nearly always a very slight trace of albumin, with larger amounts when blood was present. Occasionally there was a granular cast. In March a few red cells were occasionally found in catheter specimens. From May 17 to June 26 red cells were nearly always present, often in large numbers. Cultures were negative.

Stool: Examinations in March, April and May were negative except for a slight positive guaiac test March 4 and 23.

Blood Cultures: February 22, March 20, and April 15 showed no growth.

Wassermann reaction on blood, negative.

The Blood: (The routine red and white counts in most instances were made by the house officers, especially Dr. Colwell, as were also the smears, which were examined later by me.)

Red counts were made about every four days, at times more often. At entrance the count was 2,104,000 and remained at about this level until after the second transfusion on March 11, when it rose to 2,784,000, falling at first rapidly, then gradually to 920,000 on March 24. On this latter date after the third trans-

fusion the count rose to 1,947,000, only to fall to 800,000 before the fourth transfusion on April 2, after which it rose to 2,100,000. On April 12 the count was 808,000 but rose on this day after the fifth transfusion to 2,320,000 and to 3,020,000 on April 28, falling to 2,440,000 May 17. Small rises and rapid falls followed the transfusions of May 18, 23, and 27, so that the count was 1,800,000 after the eighth transfusion which took place May 27. After the ninth transfusion, May 29, the count was 3,664,000. A fall to 1,096,000 occurred by June 11, on which day the tenth transfusion was done and the count rose to 2,664,000 falling by July 3 to 1,424,000, and after the eleventh transfusion on this day to 3,184,000. On August 11 the count was 2,720,000.

The hemoglobin varied from 65 per cent. to 20 per cent., fluctuating with the red count so that the color index was usually below 1, though sometimes 1. After transfusion the hemoglobin rose relatively more than the red count.

White counts were made frequently. On February 17 the white count was 15,600, on February 21, 7000 and remained at about this latter figure until March 12 when it rose to 11,000 and to 16,200, March 16, falling to 10,000 on March 20. On March 29 it was 22,000, becoming 7000 April 2. During April and May it was always above 6000, usually about 9000 to 11,000. June 16 and 30 the count was 8000 and 16,000 respectively. On August 11, 6400.

Study of Stained Smears and Differential Count. Smears stained by Wright's stain were studied about every ten days. The fresh blood stained with brilliant cresyl blue was studied when the reticulated cells were counted. (See below.)

The red cells always showed considerable achromia, some poikilocytosis most marked when the red count was lowest. There was a tendency to diminution in size. Polychromatophilic cells never appeared in large numbers, though more numerous after March 13. Rarely were any stippled cells found. In counting 100 white cells, two normoblasts were found April 12 and August 11 and one on March 15. Very rarely was a normoblast seen at other times, never megaloblasts.

Platelets were absent in the smears or exceedingly rare.

The white cells showed no striking abnormality. The percentage of polymorphonuclear neutrophiles varied from 72 to 54 per cent., and the small lymphocytes from 21 to 39 per cent. A higher percentage of polymorphonuclears occurring with the higher white counts, though often some of the lower counts gave 60 to 65 per cent. of polymorphonuclears. The large lymphocytes and mononuclears varied from 2 per cent. to 7 per cent., and the transitionals from 1 per cent. to 5 per cent. Mast cells were rarely found. Usually there were no eosinophiles seen, though they rarely formed 1 per cent. or 2 per cent. On March 15, April 12, and May 17 a single myelocyte was found on searching several smears.

Exceedingly rarely was there a Howell-Jolly body seen.

The Arneth picture remained normal or showed a slight shift to the left, not as has been found in pernicious anemia by Briggs[3] a shift to the right.

Treatment of the Case. While the patient was in the hospital she was in bed except from April 27 to April 30, eating most of the time plentifully of a generous mixed diet. At times she received small doses of simple remedies to alleviate headache, nausea, constipation, etc.

Her chief treatment consisted of repeated transfusions by Dr. Leland from a donor belonging to the same isoagglutinin group[4] (Group IV). The transfusions were done by the indirect method except the second one. The effect of the transfusions may be seen by following the clinical notes. When the situation seemed hopeless the pelvic organs[5] were removed; though checking the hemorrhage through the vagina, this did not affect the disease.

In the literature there are instances in which transfusion has apparently cured purpura hemorrhagica, but also other instances where it has failed, and our case serves as an example to show that even in spite of persistent transfusion the outcome may be fatal. On the contrary, persistent transfusion may restore the patient to health, as was seen in a case of benzol poisoning[6] with symptomatic purpura hemorrhagica. The clinical picture, for about six weeks during which time five transfusions were done, was very similar to our present case. This case of benzol poisoning in contrast to ours then began to slowly but persistently improve.

On May 21 our patient received a massive dose of Roentgen rays, but this did not result in any benefit.

Locally for the bleeding from the gums and vagina at various times, solutions of different astringents were tried, but without any very striking effect.

Thromboplastic substances accelerate the coagulation of the blood and may perhaps be of value in checking hemorrhage. Two such substances were tried on this patient; "kephalin"[7] (the active thromboplastic substance) from sheeps' brains and "coagulen,"[8] a substance derived from blood platelets. Tests made *in vitro* showed that kephalin has a slightly stronger thromboplastic action than coagulen. During May, solutions of kephalin were applied to the gums and also sprayed into the vagina. This sub-

[3] Am. Jour. Med. Sc., 1914, cxlviii, 143.

[4] Moss, Johns Hopkins Hosp. Bull., 1910, xxi, 63.

[5] A case is mentioned by Ottenberg and Libman, Am. Jour. Med. Sc., 1915, cl, 36, where removal of the uterus was beneficial.

[6] Minot, Denny and Davis, Arch. Int. Med., 1916, xvii, 101.

[7] "Kephalin," a wax-like substance was prepared according to Howell's method (Am. Jour. Physiol., 1912, xxi, 1), and dissolved in cold water when desired for use.

[8] "Coagulen" is an expensive commercial preparation made by the Gesellschaft f Chemische Industrie in Basel and sold under the trade name of "Coagulen Ciba," or "Coagulen Kocher Fonio."

stance acted better than any astringents, it checked bleeding by allowing clots to form rapidly. However, the effect was but temporary, lasting only until the clot was loosened mechanically or by blood exuding behind it. Attempts were made to have the patient take kephalin by mouth, but after a few doses it proved so nauseating to her that it was not continued.

Coagulen, which Fonio[9] has enthusiastically recommended for its ability to check any sort of hemorrhage or hemorrhagic disease, was given (5 gm. in 300 c.c. of salt solution subpectorally) June 25 and 30, followed by improvement in the patient's condition. Though improvement occurred coincident with the giving of coagulen, we feel that it was by no means wholly due to this substance. In some conditions, however, thromboplastic substances are of very distinct benefit for controlling hemorrhage.

THE PLATELETS. Denys's[10] observation in 1887 that the blood platelets are reduced in purpura hemorrhagica has been verified numerous times.

The blood platelets of our patient were counted by Wright and Kinnicutt's[11] method.[12] Daily counts were made during the first ten days and sometimes after this; more often counts were made every few days except in June. The count was always abnormally low, lowest at the times of the greatest bleeding, as Duke[13] found in his cases.

On entrance, February 17, the count was 1200, at which time the bleeding was severe. As the bleeding checked the count rose to 10,000 February 20 and to 26,000 February 24. With the recurrence of bleeding the count fell and remained about 1000, with a very slight rise after the transfusion of March 8. Before transfusion March 11 the count was 8000 and the following day, when there was distinctly less bleeding it was 70,000. A gradual fall took place in the following days, reaching 22,000 March 17 and 8000 March 20, when the bleeding again increased and the previous low level of 1 to 2000 was reached on March 23; after the transfusion on March 24 the count rose to 42,000, and there was less bleeding. In five days the count fell to 2000, bleeding increased, and the count remained at this level until after the fourth transfusion April 2, when it reached 118,000 and the bleeding was checked. A rapid fall to 4000 occurred in the next four days, when the bleeding increased markedly. A temporary rise to 26,000 occurred on April 7, without any change in the amount of bleeding, which was followed by a fall in the count. Following the fifth transfusion, April 12, the count rose to 120,000, reaching 75,000

[9] Mitt. aus dem Grenz. der Med. u. Chir., 1914, xxvii, 642.
[10] La Cellule, 1887, vol. iii. [11] Jour. Am. Med. Assn., 1911, lvi, 1457.
[12] In vital stained smears the platelets seemed slightly more plentiful than the counts indicated.
[13] Loc. cit.

April 15, and remained above 46,000 until April 30, when it was 16,000. During this period of higher counts there was essentially no bleeding. From May 2 to May 17 the count fluctuated between 10,000 and 50,000, during which time there was continued and increasing bleeding. There was no appreciable change in the count three days or five days after the sixth transfusion May 19, nor diminution in the bleeding. On May 24, the day following the seventh transfusion, the count was 60,000, the gums stopped bleeding, but the vaginal flow persisted. On May 27 the count was 3000. The only other counts in June were made on the 4th and 11th, when they were 20,000 and 6000 respectively. On August 14 the count was 12,000.

Duke[14] has shown that the life of the platelets is probably but a few days, and that the improvement after transfusion of cases with very few plates lasts for but a few days or until the platelets introduced have disappeared, unless the transfusion is successful in permitting the patient to supply or not destroy his own platelets and thus not return to his previous state of bleeding.

Such effect of transfusion on the platelets is seen in our patient after some transfusions, while after others the platelets increased very slightly or for a much shorter time. Perhaps this was because not enough blood was transfused or because there was something in the patient's blood that rapidly destroyed the foreign platelets. From the *in vitro* experiments described below this latter assumption would not seem true, but reactions *in vitro* are often not the same as *in vivo*. In a case reported by Drinker and Hurwitz[15] some transfusions were also not followed by a rise in the platelet count.

Le Sourd and Pagniez,[16] Ledingham and Bedson,[17] and Lee and Robertson[18] have shown that rabbits can be immunized against guinea-pig platelets; and that the serum from such rabbits (antiplatelet serum) will cause in dilutions as high as 1 to 328 macroscopic agglutination and lysis of normal platelets, while normal rabbit serum sometimes causes this only at times and in no greater dilution than 1 to 6. Animals inoculated with antiplatelet serum develop purpuric skin lesions, bleeding from the mucous membranes, a markedly diminished platelet count, and a delayed bleeding time. The coagulation time is but slightly altered and the clot does not retract. This condition resembles closely what is seen in cases of purpura hemorrhagica. The serum from animals injected with antiplatelet serum has no abnormal agglutinative or lytic action on the platelets *in vivo* or *vitro*.

In order to find out what effect our patient's serum had on platelets the following experiments were done. Washed and

[14] Jour. Exper. Med., 1911, xiv, 265.
[15] Arch. Int. Med., 1915, xv, 733.
[16] Jour. de physiol et de path. gén., 1911, xiii, 56.
[17] Lancet, 1915, i, 311.
[18] Lee and Robertson, Jour. Med. Res., 1916, xxxiii, 323.

unwashed salt solution suspensions of platelets were obtained twice from a normal person and once from a case of purpura rheumatica with a platelet count of 290,000. Both of these individuals belonged to iso-agglutination group IV, to which our patient also belonged. To a series of tubes containing dilutions of from 1 to 3 to 1 to 120 of the serum from each of these individuals and the serum from our case there was added separately a few drops of each platelet suspension. In none of the tubes was there any macroscopic evidence of abnormal lysis or agglutination of the platelets. In the tubes with unwashed platelets clotting occurred in the lower dilutions, showing fibrinogen was present.

Similarly suspensions of platelets were obtained from our patient when her platelet count was 60,000 and also from a normal person and added separately to the serum of both. There was the slightest suggestion that the patient's platelets after one hour were abnormally agglutinated by either serum.

Bleeding Time. Duke[19] observed that with a much reduced platelet count bleeding from a small puncture occurred for an abnormally long time. He blotted up on absorbent paper, at frequent intervals, the blood that flowed from a small puncture in the lobe of the ear. The duration of such a hemorrhage he called the bleeding time. The bleeding time of our patient from an ear prick of as near the same size as possible each time was determined by Duke's method, as often as the platelets were counted, sometimes more often. As has been noted by Duke,[20] [21] this time fluctuated with the number of platelets. A normal bleeding time of under three minutes occurred only when the count was above 60,000 excepting following the transfusion of March 24 when the count was 42,000. When the count was 1 to 5000 the bleeding time varied from a maximum of two to three hours even up to four hours March 10 (when a clamp was used to stop the bleeding) down to fifty to thirty minutes. When the count was 5 to 14,000, it varied from forty to twelve minutes. When 18 to 32,000, from eight to twenty minutes usually eight to twelve minutes, with the few counts between 46 to 60,000 about six minutes.

A difference of one or two minutes occurs in the normal bleeding time, and Duke[22] [23] has pointed out that no matter what the size of the puncture is this time will vary little. This seems to be true of normal cases; however, in this case where there was pathological bleeding time, I have noticed that the bleeding time was distinctly longer with a larger than a smaller puncture, a difference of thirty and fifty minutes frequently appeared.

Besides determining the bleeding time from the ear it was determined five times from a vein puncture in the forearm. Three times when the bleeding time from the ear was forty minutes to

[19] Loc. cit. [20] Loc. cit. [21] Loc. cit. [22] Loc. cit. [23] Loc. cit.

one and a half hours it was twenty to fifteen minutes from the arm and when two and a half minutes from the ear was thirty seconds from the arm.

Aynaud[24] found in normal animals about the same number of platelets in different arteries and veins. Nevertheless, it was thought that this difference of bleeding time from the capillaries of the ear and the vein of the arm might be due to a difference in the platelet count, but no special difference was found.

Attempts to Inoculate Animals. Besides the production of purpura hemorrhagica in animals by antiplatelet serum it has been produced by various poisons[25] that evidently act on the bone marrow as benzol, diphtheria toxin, tuberculin, etc.

Production of purpura by the injection of blood from patients into animals was accomplished in 1884 by Petrone[26] and in 1892 by Charrin.[27] However, they obtained positive cultures from the patients and animals of the same organism which was hemolytic in nature. Marchetti,[28] in 1910, also obtained from cases of purpura organisms that produced purpura in animals. Organisms of various sorts have been reported from cases exhibiting purpura, but there are many purpuric cases in which no organism has been found. Grenet[29] obtained purpura in rabbits by creating an hepatic lesion by temporary stasis of blood in this organ and injecting serum from purpuric and hemophilic patients into the spinal canal. His work was repeated with negative results by Crowell,[30] who also got no reduction of the platelet count by injections of benzol. Whether these various cases of purpura whose blood or the organisms from whose blood produced purpuric symptoms in animals had a much reduced platelet count, and therefore were cases of purpura hemorrhagica, is not known.

Injections of serum and blood from our patient into animals were unsuccessful in producing any purpuric manifestations.

Two rabbits of about 1200 gm. were each given intravenously for five days fresh serum collected within two hours previously. The first received three 2 c.c. injections and two 1.5 c.c. injections, and was found dead on the sixth day. Autopsy showed only an enlarged soft spleen and microscopically bacteria. Cultures were not made. The second rabbit received three 2 c.c. injections and two 1.6 c.c. injections, and remained well even after four months. Daily platelet counts, though fluctuating somewhat, were within normal limits in both animals. The white count in the second rabbit

[24] Arch. d. mal. du. cœur, 1911, iv, 358.
[25] Duke, Arch. Int. Med., 1913, xi, 100.
[26] Quoted in Nothnagel's System of Prac. Med., Am. ed., 1905, xi, 745.
[27] Compt. rend. Soc. de biol., 1902, liv, 427.
[28] Reviewed in Arch. d. mal. du cœur, 1911, iv, 466, from Congress de Méd. Int. Rome, December, 1910.
[29] Thèse de Paris, 1905, Jules Rousset, publisher.
[30] British Med. Jour., 1912, ii, 1102.

remained normal, as has been noted by Moss and Brown[31] after serum injections. The white count rose in the rabbit that died.

Loeb, Strickler, and Tuttle[32] have shown that about 6 to 10 c.c. of human serum per kilo of body weight rapidly kills when given intravenously. The serum from our patient was no more toxic for rabbits than normal serum, for 5 c.c. of normal human serum killed a 1100 gm. rabbit in six minutes and 4.5 c.c. of serum from our patient killed a 1120 gm. rabbit in one and a half hours.

With Dr. Sellard's help a monkey of about 3 kilos, while under ether, was given intrasplenically (after opening the peritoneum) by indirect transfusion about 13 c.c. of blood from our patient. This animal developed no abnormal symptoms after four months, and the formed blood elements and coagulating factors when examined after ten days were quite normal.

In view of the fact that blood cultures from the patient were negative, that the rabbit receiving serum from the same lot and in larger amounts than the rabbit that died remained well, and that the monkey did also, it is felt that death of the first rabbit from infection was due to faulty technic.

Were the case of purpura hemorrhagica similar to the purpura produced by antiplatelet serum in animals, the negative results obtained from injecting the patient's serum and blood into animals and from the tests for lysis of the platelets would be comparable to the negative results upon platelets obtained with serum of the purpuric animals *in vivo* and *in vitro*. This supposition may be true but has not been proved.

The Reticulated Red Cells. The reticulated red blood cells (cells with a granulofilamentous substance stained by treating fresh blood with brilliant cresyl blue) were counted by the following method used by Hawes[33] and suggested by Wright.

A drop of freshly prepared solution of brilliant cresyl blue 1 to 1400 was dried on a microscope slide. Upon this dried stain was placed a drop of blood on a cover-glass. One thousand or two thousand red cells were counted in an area of the preparation, which was stained not too deeply or lightly, and the percentage of reticulated cells noted.

These cells are considered young cells. Their number and character give us a direct insight into the hemopoietic activity of the marrow. They normally comprise not over 1 per cent. of the red cells.

The reticulated cells in our case comprised on four different days between February 22 and March 6, 10 to 14 per cent. of the reds, which at this time averaged about 2,100,000. Before transfusion, March 11, they were 15 per cent., and the next day 10 per

[31] Johns Hopkins Hosp. Bull., 1911, xxii, 258.
[32] Virchows Archiv., 1910, cci, 5.
[33] Boston Med. and Surg. Jour., 1909, clxi, 493.

cent., rising to 19 per cent. March 15. Between March 17 and 24 they were 12 to 13 per cent., during which time the red count fell, reaching 920,000. Shortly after the transfusion on March 24, when the red count rose to 1,947,000, they were 8 per cent., rising to 15 per cent. March 27, when the red count had fallen to 1,043,000 and to 16 per cent. when the red count was 800,000. A similar though less marked fall and rise followed the transfusion of April 2. After this transfusion, when the red count was 2,320,000, the reticulated cells formed 5.25 per cent. of the reds. During the next eighteen days, as the red count rose, they formed about 7 per cent. of the reds. As the red count fell in early May the reticulated cells were usually about 10 per cent. They were then not counted until May 29, when after the transfusion on this day they were 9 per cent. and on June 15, 12 per cent., and August 14, 7 per cent.

These cells were always present in abnormally high numbers, higher when the red count was lower, a time when one would expect a greater effort on the part of the marrow to regenerate blood cells. Shortly following transfusion there was a drop, followed a few days later by a rise which would be expected if the transfused blood acted to stimulate the marrow. Vogel and McCurdy[34] have observed this effect of transfusion on the reticulated cells in cases of pernicious anemia.

Reports on the condition of the marrow in cases of purpura hemorrhagica with low platelet counts are rare. Hyperplastic myeloid and aplastic marrow are reported. It seems that cases presenting the symptoms of purpura hemorrhagica due to aplasia of the marrow (as evidenced by a leukopenia, lymphocytosis, and diminished or absent reticulated cells) are more properly cases of aplastic anemia, and that purpura hemorrhagica not complicating other diseases and without known etiology but without evidence of aplastic marrow belongs to another group.

Vogel and McCurdy[35] cite a case of purpura hemorrhagica that had no reticulated cells, a marked leukopenia, and that did not respond to transfusion. Though the bleeding in this case was evidently similar to ours, the percentage of the reticulated cells and the white count were the opposite. Their case perhaps would be more properly called one of aplastic anemia, with symptomatic purpura hemorrhagica.

Vasquez[36] pointed out that the disappearance of reticulated red cells in pernicious anemia is a strong argument for the diagnosis of aplastic changes in the marrow. That a marked reduction or absence of these cells speaks for an aplastic marrow has been also emphasized by Pepper and Peet[37] and Musser.[38]

[34] Arch. Int. Med., 1913, xii, 707.
[35] Loc cit.
[36] Bull. et mém. Soc. méd. d'hôp. de Paris, 1907, xxiv, 1532.
[37] Arch. Int. Med., 1914, xii, 81.
[38] Ibid.,xiv, 275.

The reticulated cells were diminished in two cases with aplastic marrow that I have studied. One, a case of aplastic anemia proved at autopsy, showed no reticulated cells in several smears. The other, the case mentioned before of poisoning with benzol (a substance that produces aplasia of the marrow) showed at first an exceedingly rare reticulated cell, but after the fifth transfusion when the case improved, the reticulated cells were 3 per cent.

Vogel and McCurdy[39] consider that the total absence of reticulated cells in their case showed complete inability of the marrow to respond to stimulation by transfusion, which with the low white count would most certainly suggest an aplastic marrow. That cases with aplastic marrow have a very low percentage of reticulated cells seems certain. Such cases may have purpura hemorrhagica due to the aplasia. Our case does not fall into this group on account of the constant high percentage of reticulated cells, no leukopenia, often a leukocytosis, and no marked lymphocytosis.

The reason for the very low platelet count in our case might perhaps have been due to some localized aplastic condition of the platelet forming elements, which in turn might have been due to some specific poison. It seems very unlikely that there was any aplasia of the elements that form the red or white cells. If there was no localized aplasia it seems that the low platelet count was due to some specific reaction (presumably a specific poison) that destroyed the platelets as fast as they were formed. Possibly there was a combination of a localized aplasia and a destruction of formed platelets as the cause for the low platelet count.

Coagulation of the Blood. Normal, decreased, and increased coagulation time of the whole blood are reported in cases of purpura. Such conflicting reports are probably due to different technics and different types of purpura at different stages of the disease.

In the cases with low platelet counts, Duke[40] has found a normal coagulation time. Other observers give increased or normal coagulation time for these cases.

There have been few determinations of prothrombin and antithrombin in such cases.

Austin and Pepper[41] and Whipple[42] found an antithrombin increase. Minot, Denny and Davis[43] found the antithrombin normal or slightly above or below normal. Howell[44] found no abnormality.

In experimental benzol poisoning with reduced platelet counts, Hurwitz and Drinker[45] have shown that there is a lessened amount of prothrombin which does not always vary directly with the number of platelets. The antithrombin was normal.

The oxalated plasma from Lee and Robertson's purpuric animals

[39] Loc. cit. [40] Loc. cit. [41] Arch. Int. Med., 1913, xii, 637.
[42] Ibid., xi, 305. [43] Loc. cit.
[44] Ibid., 1914, xiii, 76. [45] Jour. Exper. Med., 1915, xxi, 401.

which I examined showed a slightly delayed prothrombin time with normal antithrombin.

Minot, Denny and Davis[46] noted that cases with low platelet counts may or may not have a delayed coagulation time, and that with the delayed coagulation time there was a delayed prothrombin time. They felt that perhaps cases with excessively few plates always had a somewhat delayed coagulation time.

Determinations of the coagulation time, prothrombin and antithrombin were made in our case and the results given in Table I.

The coagulation time was determined by the method described by Lee and White,[47] normal being five to nine minutes. With the low platelet counts the clots were non-retractile and weak. The clot on April 15, when the platelet count was higher, retracted very slightly.

The prothrombin and antithrombin were determined by Howell's method as discussed by Minot, Denny and Davis.[48] The test for prothrombin is one for its relative efficiency, and consists of determining the time (prothrombin time) that it takes an oxalated plasma to clot on recalcification with the optimum amount of calcium; that is, the amount that causes the most rapid clotting.

As the table shows, the blood of our case had a delayed coagulation time associated with a delayed prothrombin time, with one exception when both were normal. These times, though usually but slightly abnormal, were once quite markedly so. They did not vary directly with the platelet count or clinical symptoms. The antithrombin was normal. The fibrinogen was not determined accurately, but was probably not markedly diminished, as was told by the amount of precipitate formed on heating the plasma to 60° C.

TABLE I.

Date.	Coagulation time (minutes), case.	Coagulation time (minutes), control.	Prothrombin time (minutes), case.	Prothrombin time (minutes), control.	Antithrombin factor.	Platelet count.	Clinical condition.
Feb. 17 A.M.	23	8½	30	12	1.2	1,200	Very marked bleeding.
Feb. 17 P.M.	27	8	26	12	..	..	Very marked bleeding.
Feb. 20	20	8	20	12	1.2	10,000	Marked bleeding.
Feb. 22	11	9	15	11	0.8	22,000	Very little bleeding.
Feb. 23	11½	9	16	13	1.0	..	Very little bleeding.
Feb. 25	20	8	20	12	..	26,000	Very little bleeding.
Mar. 1	18	9	25	14	..	5,000	Marked bleeding.
Mar. 6	10	7	15	12	1.1	1,600	Very marked bleeding.
April 15	6	8	8	8	0.87	75,000	No bleeding.

[46] Loc. cit. [47] Am. Jour. Med. Sc., 1913, cxlv, 495. [48] Loc. cit.

Other studies were made on the coagulation of the blood, some of which are as follows. The first was done by Dr. Lee.

1. Washed and unwashed platelets were found to have fully as much thromboplastic activity as normal platelets. This agrees with Fonio's[49] hypothesis that though the plates are lacking in numbers in this disease, they are not lacking in activity.

2. Salt and water extracts of the uterus accelerated the clotting of normal oxalated plasma. There was thus no evidence of deficient thromboplastic activity as a cause for bleeding.

3. The syphilis coagulation test as described by Hirshfeld and Klinger[50] and also Fränkel and Thiele,[51] which gives a marked delay in syphilis, was done twice. Both times there was a slight delay, but no such marked delay, as is seen with syphilis.

4. Howell[52] has recently studied the clotting of blood under the ultramicroscope and has found different appearances of the fibrin needles under different conditions. He suggested that perhaps one might detect abnormalities of the blood in disease by this method. Dr. Howell very kindly studied the clotting with thrombin of a specimen of oxalated plasma from our case, but was unable to detect any abnormality. On another specimen I likewise found by this method the clotting to appear normal.

THE TOURNIQUET SIGN. The effect of placing a tourniquet about the arm for three minutes so that the return blood flow is shut off was studied. This test is considered a test for the manifestation of diminished resistance in the walls of the smaller blood-vessels. Frugoni and Guigni[53] believed that this test was positive in cases with a tendency to hemorrhagic manifestations.

Morandi[54] has studied the test and has found it positive in a wide variety of diseases. Hess[55] has found it positive in cases of scurvy. In describing the test, Hess states that "after the pressure is removed and the arm loses its cyanosis one looks for petechiæ below the point of constriction, but no importance should be attached to minute petechiæ that appear just below the pressure band as these are often found in normal cases." In our case the test was done with these precautions.

On February 16, when there were many purpuric spots on the skin, this test was strikingly positive, spots even as large as a ten-cent piece appearing rapidly in the skin below the tourniquet. On the following days, as the lesions all over the skin faded, the test became practically negative, reappearing with the recurrence of fresh spots on the body.

[49] Mitt. a. d. Grenzeb. d. Med. u. Chir., 1914, xxviii, 313.
[50] Deutsch. med. Wchnschr., 1914, xl, 1607.
[51] München. med. Wchnschr., 1914, lxi, 2095.
[52] Amer. Jour. Physiol., 1914, xxxv, 143.
[53] Semaine méd., 1911, xxxi, 25.
[54] Summary, Jour. Am. Med. Assn., 1912, lix, 1555.
[55] Am. Jour. Dis. Child., 1914, viii, 386.

Following the transfusion, March 8, the patient developed no skin lesions until May 11, a time when she had gone the longest during her hospital career without a transfusion. From March 8 to May 11 there appeared rarely a few minute spots on the arm below the tourniquet (no tests between April 25 and May 10), and during the following week, when purpuric skin lesions reappeared, the tourniquet sign was positive, though not as striking as in February. After the transfusion May 18 and until the patient left the hospital July 4 there were no noteworthy skin lesions, seldom a positive tourniquet sign, and then of slight degree. However, on August 14, when the patient had had no transfusion for even a longer period than when in the hospital, and there were purpuric spots scattered on the arms and legs, the sign was present but not striking. Thus the most positive tourniquet sign occurred when there were spontaneous purpuric spots on the skin. Whether the transfusions had any effect in preventing recurrence of skin lesions cannot be told until other cases are studied.

MISCELLANEOUS STUDIES. 1. Both Goodpasture[56] and the work of Gley and Le Bas[57] suggested that there might be a fibrinolytic ferment in the blood of purpura hemorrhagica cases. Goodpasture[58] has shown that such a ferment exists in the blood of cases of atrophic cirrhosis. However, no fibrinolytic ferment was found in our case.

2. Robertson determined by Wilbur and Addis's[59] method the urobilin content of the stools during the week of April 15. He found no abnormality, thus indicating there was no increased blood destruction.

3. On several occasions the hydrogen ion concentration of the blood was determined by the method described by Levy, Rowntree and Marriott[60] and by a slight modification of this method. In all instances the concentration was normal.

4. The fragility of the washed red corpuscles was tested by means of various strengths of salt solution. Both the patient's and normal red cells began to hemolyze in 0.45 per cent. salt solution. The patient's cells were completely hemolyzed in 0.26 per cent., and the controls in 0.30 per cent.

SUMMARY AND CONCLUSIONS. A case of idiopathic purpura hemorrhagica, occurring in a girl of eighteen is presented. The case had an abnormally low platelet count which is typical of this condition. The low platelet count seemed to have been due to one or both of the following two factors:

1. Some reaction (presumably a specific poison) taking place in the body which destroyed the platelets as fast as they were formed.

2. A localized aplasia of the platelet-forming elements of the marrow which might have been due to some toxic phenomena.

[56] Personal Communication.
[57] Arch. de physiol. norm. et path., 1897, ix, 848.
[58] Johns Hopkins Hosp. Bull., 1914, xxv, 330.
[59] Arch. Int. Med., 1914, xiii, 235.
[60] Ibid., 1915, xvi, 389.

This destructive process, perhaps toxic, anaphylactic, or of some other nature, seems to have been specific because none of the other formed blood elements were involved.

The anemia was easily explained by hemorrhage. There was no evidence of red cell destruction as shown by the urobilin tests. The white cells were not affected.

The case was not one of aplastic anemia, *i. e.*, with generalized aplasia of the marrow, because there was no leukopenia, no marked lymphocytosis, and there was always a high percentage of reticulated red cells. In cases with aplasia of the bone marrow these cells are absent or very rare, and when increased probably signify activity of the red cell elements of the marrow.

The specificity of this reaction on the platelets simulates in every way animals injected with antiplatelet serum.

In vitro the patient's serum caused no abnormal lysis or agglutination of normal platelets.

Injections of patient's serum and blood into animals were negative.

There was usually a delayed coagulation time, a weak, non-retractile clot associated with a delayed prothrombin time which did not vary directly with the platelet count or clinical symptoms. The antithrombin was normal. The platelets were actively thromboplastic as were extracts from the uterus. Very slight delay of coagulation occurred with the syphilis coagulation test. The clotting of the plasma with thrombin as seen under the ultramicroscope was normal.

The tourniquet sign was greatest when there were spontaneous purpuric lesions on the skin.

The bleeding time varied with the platelet count becoming longer as the platelets diminished.

The bleeding time was longer with a larger than a smaller puncture.

The bleeding time from the arm vein was shorter than from the ear, which was not due to a difference in the platelet count.

The essential treatment consisted of trying to replace the lacking platelets by eleven transfusions of normal blood and by giving locally and subcutaneously thromboplastic substances which contain one of the active principles of platelets.

Transfusion resulted in, usually but not always, temporary improvement of the patient's condition, in turn associated with a temporary rise of the platelet count.

Thromboplastic substances were perhaps of benefit in temporarily controlling hemorrhage.

In spite of the persistent therapeutic procedures the course of the disease was very little affected, and the patient died thirteen months after the onset of her illness.

THE SPINAL-FLUID SYNDROMES OF NONNE AND FROIN AND THEIR DIAGNOSTIC SIGNIFICANCE.

By Frederic M. Hanes, M.A., M.D.,
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G. Froin[1] reported in 1903 three cases which upon lumbar puncture showed spinal fluids yellow in color (xanthochromia), containing numerous cells, and which, upon standing, coagulated spontaneously and massively, owing to their high fibrin content. The phenomena thus described were new to medical literature, and they have since been collectively designated "Froin's syndrome." Later observers, using more accurate methods of cell enumeration, have not confirmed Froin's finding of "numerous cells," and pleocytosis cannot be regarded an essential part of the syndrome. This point will be discussed later.

Some five years after Froin's publication, M. Nonne[2] reported three cases of cord tumor, the spinal fluids of which contained an excess of proteid (strongly positive phase I) with no leukocytosis (pleocytosis) of the fluids. Nonne was unable to interpret the dissociation of proteid excess and pleocytosis in his three cases, and did not feel from his limited experience that any positive diagnostic significance could be attributed to the syndrome in relation to spinal-cord tumors.

Since the appearance of these two contributions the literature has been augmented by several papers dealing with either one or the other of these two syndromes, but no one has suggested that they are closely related phenomena. In this communication we shall bring forward evidence, both from our own experience and the literature, with the object of proving that the syndrome of Nonne is simply the early manifestation of a process which in its later and terminal phases gives rise to the syndrome of Froin. We shall try, furthermore, to show that the Nonne-Froin syndrome when properly interpreted is of the greatest practical assistance in the differential diagnosis of spinal-cord lesions.

Xanthochromia, or yellow pigmentation of the spinal fluid, has been described by many observers, and cannot be regarded as a rarity. We have seen five instances of this condition in the past three years. It is such a striking and unexpected finding at lumbar puncture that it has assumed a larger share of importance than it deserves. It will be necessary to define clearly the exact condition which can properly be termed xanthochromia, for hemorrhage into the cerebrospinal fluid from ventricular apoplexy, traumatic rup-

[1] Gaz. d. hôp., 1903, 000, 000.
[2] Quoted by Raven, Deutsch. Ztschr. f. Nervenk., 1914, xliv, 380.

ture of meningeal vessels, or other causes leads to a condition which has been designated erythrochromia, and this hemorrhagic pigmentation has been frequently confused with xanthochromia. The two conditions possess certain characteristics which permit of their ready differentiation.

1. The color in erythrochromia varies from a bright red through varying shades of reddish-brown, reddish-yellow to a dark yellow color. Lumbar punctures made at intervals of several days on a case with hemorrhagic spinal fluid have shown a variety of color changes (Schwarz), whereas the color in xanthochromatic fluids remains the same from puncture to puncture. The shades in xanthochromia are described as amber, cream, or straw colored, and instances are recorded in which the color remained the same throughout several months.

2. In erythrochromatic fluids red blood cells or their shadows may be very numerous. In a case which we saw recently, in which the patient had fallen upon his head from a swiftly moving automobile, the spinal fluid was the color of arterial blood and red blood cells were present in very large amount. From this extreme picture lesser grades of erythrocytosis are found, and finally only shadows of red cells or a reddish-yellow pigmentation remains as evidence of former hemorrhage. Such fluids, however, yield positive chemical test for blood, although in later stages the spectroscope may fail utterly to reveal characteristic bands. Furthermore, owing to the meningeal irritation of the products of red-cell destruction, a leukocytosis of the fluid develops. Schwarz reports such a case in which there were numerous shadows of red cells and 268 white cells (mostly lymphocytes) to the cubic millimeter of fluid. In xanthochromia the white cells are, as a rule, not increased; there are no red cells, and the fluid does not yield either chemical or spectroscopic evidence of hemoglobin derivatives. When the white cells are increased it is evidence of meningeal inflammation.

3. The fibrin content of xanthochromatic fluids is extremely high. The citron-yellow fluid, which is quite limpid, coagulates spontaneously, and in so massive a manner that the containing test tube can be inverted without loss of its contents. The coagulum is gray or white. This is not true of erythrochromatic fluids. They may contain fibrin to a certain extent, but they do not coagulate massively.

4. Both xanthochromatic and erythrochromatic spinal fluids contain proteid substances in very large amount, but whereas in xanthochromia a large excess of proteid is a constant and characteristic part of the picture, in erythrochromia the proteid tends to decrease in amount the further away in time from the hemorrhage the fluid is removed.

In purulent meningitis the spinal fluid may be colored yellow, brown, or green, but there is no danger whatsoever of confusing

such a finding with any other, owing to the presence of pus cells in enormous amounts and of bacteria.

The syndrome of xanthochromia with massive coagulation of the spinal fluid and high proteid content, with or without pleocytosis, is always produced by a localized obliteration of the pia-arachnoid space which divides it into two parts, an upper one in free communication with the pia-arachnoid spaces of the upper cord and brain and a lower cul-de-sac. In this lower cul-de-sac the fluid gradually changes in character from the normal limpid spinal fluid to the xanthochromatic type of fluid just described. The following briefly summarized case will illustrate perfectly the conditions leading to the xanthochromia-syndrome:

A child of nine months was admitted to the hospital suffering from spastic paralysis of both arms and legs. Upon the least stimulus the arms, legs, and trunk would pass into a tetanic spasm. Lumbar puncture revealed a fluid the color of picric acid, containing sixteen cells to the cubic millimeter, a very great excess of proteid, and the fluid coagulated massively on standing. After a few days it was observed that the child's fontanelles were bulging markedly, and to relieve the tension a needle was inserted through the anterior fontanelle and 30 cm. of perfectly normal limpid cerebrospinal fluid was withdrawn. This fluid contrasted strongly in every way with that removed by lumbar puncture.

The child died, and at autopsy a large mass of tuberculous granulation tissue was found completely encircling the medulla and quite obliterating the pia-arachnoid space at the level of the foramen magnum. The mass of new growth had completely separated the pia-arachnoid spaces of the cord from those of the brain.

Another instance of the syndrome under discussion was seen recently in a man, aged twenty-seven years, who for a year had suffered from a painlessly developing paraplegia which had terminated in an utter spastic paralysis of both legs. The history and physical findings indicated cord compression at the level of the seventh dorsal segment, and at operation a cyst of the pia-arachnoid was discovered which was completely obliterating the pia-arachnoid space and compressing the spinal cord. Below the site of this compression the veins of the pia were much engorged and tortuous. The cyst was drained, and six weeks after operation a lumbar puncture revealed a fluid normal in every respect. The paraplegia improved remarkably following operation.

Three other instances of the xanthochromia syndrome which we have studied were in cases of extramedullary spinal-cord tumors, situated at various levels of the cord. In every instance, however there was produced by the tumor a cul-de-sac below the site of cord compression, and following the removal of the tumor the spinal fluid regained its normal characteristics.

The literature of xanthochromia with massive coagulation has

been reviewed recently by Mix.[3] He says: "Whenever the spinal fluid is found to conform to this syndrome it means that there is an isolated cul-de-sac. It may be isolated by meningitis, which has sealed the meninges to the surface of the cord, or it may be due to a pachymeningomyelitis or to a tumor which compresses intradurally, and so "cuts off by pressure the cul-de-sac, or to an intradural tumor which acts as a ball-valve, plugging up the top of the lumbar enlargement of the spinal cavity." With this statement our own experience is in complete agreement, and from this clear description of the mechanism of production of the syndrome the great practical diagnostic importance of the finding will readily be appreciated. Any pathological alteration of the vertebræ, dura mater, or pia-arachnoid which leads to partial or complete obliteration of the pia-arachnoid space and the formation of a cul-de-sac is capable of producing the syndrome of xanthochromia with excess proteid and massive coagulation. If the pathological change is associated with inflammation of the meninges there will be a leukocytosis of the fluid, but when the compression is due to non-inflammatory growths it is our experience that no pleocytosis is present. When cellular elements are present in more than normal amount, syphilis or tuberculosis should be strongly suspected.

The origin of the pigment in xanthochromatic fluids has led to some discussion. It has been suggested that the color in the last analysis is due to blood pigment from multiple small hemorrhages (Schwarz,[4] Kafka,[5] Raven[6]). We believe from our observations that the xanthochromia syndrome is produced by transudation of blood serum into the pia-arachnoid cul-de-sac, owing to stasis produced by pressure upon the veins of the pia at the site of cord compression. The high content of such fluids in fibrin and proteids, and the presence in them of few cells, supports the view that we are dealing in these cases with a transudate which is perfectly analogous to pleural transudates due to venous compression. One has only to recall the circulatory conditions in the spinal cord to realize how pressure upon the venous return flow would naturally lead to stasis with transudation. Multiple small hemorrhages, on the other hand, would produce the condition of erythrochromia, which, as we have pointed out, possesses characteristics which distinguish it from the xanthochromia syndrome.

At the beginning of this paper we stated that the findings of Nonne—namely, high proteid content with no pleocytosis—in three cases of cord tumor were closely related to Froin's syndrome of xanthochromia, with massive coagulation. It remains to make clear this connection.

[3] Murphy's Clinics, 1915, iv, 187 (full literature).
[4] Deutsch. Ztschr. f. Chir., 1913, cxxiv, 346.
[5] Ztschr. f. d. ges. Neurol. u. Psychiat., 1912.
[6] Loc. cit.

Raven,[7] a pupil of Nonne, has contributed a very valuable paper from Nonne's clinic reviewing 47 cases of cord tumor—20 from the experience of the clinic and 27 from the literature—in which the proteid content (phase I) of the spinal fluids was high with low cell count (no pleocytosis). His article is deficient in that he does not state how many of these cases showed xanthochromia and massive coagulation. That some of his cases did show these phenomena is obvious from his discussion and conclusions. In his series the findings ranged from slight proteid increase without coloration of the fluid to frank outspoken xanthochromia with great excess of proteid and massive coagulation. Although he clearly recognizes that cord compression is the cause of the proteid increase, xanthochromia, etc., he fails to make clear the all-important fact that xanthochromia with massive coagulation is but the terminal picture of a process which begins with an increase of proteid without pleocytosis as its sole distinguishing feature. In a series of spinal fluids from cord-compression cases every gradation can be traced from proteid excess alone to marked xanthochromia with an enormous excess of proteid and massive coagulation.

Mestrezat in his monograph on the cerebrospinal fluid (Paris, 1912) reports nine cases which illustrate the early stages of the Nonne-Froin syndrome. He speaks of them as "les cas frustes," or imperfectly developed examples of the xanthochromia—syndrome. Some of these cases failed to show xanthochromia; others showed no pleocytosis, though yellow in color and coagulating spontaneously; still others exhibited variations in the formation of a coagulum. As one reads these cases in the light of what has been said previously in this paper, one has no hesitancy in classing them among the type of cases reported by Nonne; they represent stages more or less advanced in the Nonne-Froin syndrome.

Under the title "Dissociation albumino-cytologique an cours des compressions rachidiennes," Sicard and Foix[8] have published interesting observations upon the spinal fluids of patients suffering from active Pott's disease. They found the albumin content of such fluids abnormally high, but with no accompanying pleocytosis, and, as indicated in their title, they attribute their findings to cord compression by the tuberculous vertebræ. They likewise mention that twelve cases of cord tumor showed increase of albumin with no plecytosis. It is thus evident that compression of the cord from whatsoever cause leads to an excess of proteid in the spinal fluid, and that when the meninges are not involved, there is no abnormality in the cell count.

We are convinced that the prominence which Froin's syndrome of xanthochromia with massive coagulation has assumed in the

[7] Loc. cit.

[8] Sicard and Foix, Presse méd., 1914, xx, 1013.

literature is due to the fact that the striking yellow color and spontaneous coagulation of the fluid cannot possibly be overlooked, whereas proteid increase alone requires laboratory experience for its demonstration and interpretation. It is perfectly obvious though that if evidence of cord compression is to be obtained from the spinal fluid, it is important to elicit this evidence before the terminal phase of xanthochromia with massive coagulation is established. Proteid increase without pleocytosis has the same significance in the early stage of cord compression that the full-blown xanthochromia syndrome has in the later stage of more or less complete paraplegia. Indeed, the stage of xanthochromia with massive coagulation may never be reached, and only the early phase of proteid excess without pleocytosis exist as evidence of cord compression.

Conclusions. 1. Compression of the spinal cord and its meninges from whatsoever cause leads to the formation of a cul-de-sac, more or less complete, distal to the site of compression. This leads to characteristic changes in the spinal fluid.

2. The earliest characteristic change has been described by Nonne as an increase of proteid (phase I positive) without cell increase (pleocytosis).

3. As the condition of cord compression persists, the fluid gradually becomes yellow in color (xanthochromia), the proteid content increases enormously, and the fluid, when removed, coagulates spontaneously (Froin's syndrome). Pleocytosis may or may not be present, depending upon whether or not the meninges are inflamed by the pathological process causing the compression.

4. Xanthochromia of the spinal fluid must be distinguished from staining of the fluid by hemoglobin derivatives (erythrochromia).

5. The spinal-fluid syndrome of Nonne-Froin is very helpful and reliable in the diagnosis of spinal-cord lesions. When present it always indicates a compressive lesion of the cord.

CHYLOTHORAX. REPORT OF A CASE.

By Philip Lewin, M.D.,
Chicago.

Introduction. Chylothorax is a condition in which the pleural cavity contains chyle. This condition may be due to a rupture of the thoracic duct or its radicles, or to some pathological condition of their walls, whereby the contents may be transuded into the pleural cavity. Chyle is lymph derived from the walls of the alimentary tract.

INFREQUENCY. Handmann, writing in 1899, in reviewing the literature of 261 years, was able to collect only 41 cases of chylothorax.

Baldwin, in 1908, brought the number up to 47 cases of genuine chylothorax and 15 doubtful cases. In 1912 Sale added 1 case. In 1913 De Lange and Grunder each reported 1 case, and with the present case the total number to date is, so far as I am able to find, 51 cases in two hundred and seventy-seven years of medical literature.

There is no doubt that many more cases have occurred: some never having been diagnosed; others diagnosed but never reported. These cases have been overlooked because the condition can be diagnosed only by the exploring needle or postmortem examination.

The diagnosis depends upon four factors:

1. Physical examination.
2. Roentgen-ray examination to demonstrate fluid in the chest.
3. History of
   Trauma;
   New growth or
   Liability to obstruction.
4. Aspiration and examination of fluid.
   Chemically,
   Microscopically, and
   Biologically.

The case I wish to report is that of H. A., male, born in Sweden, aged fifty years. He entered St. Luke's Hospital April 3, 1914, on the service of Dr. R. B. Preble, having been referred by Dr. Gilbert, of Chicago Heights.

History as obtained by Dr. Cameron is as follows:

Complaint. Large abdomen.

Family History. Mother died of tumor of pelvis; nature unknown.

Past History. General health has been good. Formerly troubled with headaches and occasionally a dizzy spell on change of position. No symptoms of tuberculosis. Appetite always good. No distress after meals. No vomiting or hematemesis. No jaundice or colic. Denies venereal infection, and careful questioning does not reveal any evidence of same.

Habits. Good.

Weight. Getting poorer in flesh, but gaining in weight, since abdomen began to increase in size.

Present Trouble. One year ago patient first noticed that his abdomen was increasing in size. No pain, vomiting, or distress after eating. Appetite good. Slight dyspnea but no edema of ankles. No jaundice or colic. Abdomen continually increasing in size symmetrically.

Four months ago patient first noticed a few small subcutaneous

lumps over chest wall and abdomen. Few inguinal glands, which had always been palpable, were increasing in size. Axillary glands were growing larger and were easily palpable. No pain or inflammation.

Four weeks ago patient noticed that the scrotum and prepuce were swelling, the latter causing difficulty in micturition.

One week ago edema of ankles appeared. Patient had four or five bowel movements daily, which were black in color and fairly well formed. He never noticed any blood in the stool.

Physical examination made by Dr. C. P. Clark and the writer April 5, 1914:

General Considerations. Patient is a white male, aged fifty years, six feet tall, and 175 pounds in weight. Well developed, but state of nutrition poor at present. Circumference of chest, 36 inches; of abdomen at umbilicus, 40 inches. No marked dyspnea in the recumbent position. No apparent pain. He is able to be up and about. Skin is dry and loose except over abdomen, where it is very tense and shiny. Hair is scant and dry. No seborrhea. Acne present. No scars of any kind. No tenderness over long bones or sternum. No evidence of present or former fractures. There is an exostosis of the right ilium. The umbilicus is prominent, but there is no hernia. So far as can be determined under the abnormal condition of the scrotum there is no evidence of inguinal hernia. No femoral hernia. No evidence of present or former inguinal abscess.

Nervous System. Mental condition normal. No anesthesias or paresthesias. Knee-jerks very sluggist. Plantar, abdominal, and corneal reflexes absent; faucial reflex practically gone. Arm and jaw reflexes active. There is a coarse tremor of the lips, tongue, and fingers, but none of the head. Babinski, Oppenheim, and Gordon signs negative, also Kernig and Romberg. No ankle clonus. Pupils equal and react to light and accommodation. No strabismus or nystagmus.

Ears. Air conduction on left side very poor. Bone conduction poor on both sides.

Circulatory System. Blood-pressure: systolic, 138; diastolic, 92; pulse-pressure, 46. Moderate sclerosis of all superficial arteries. Veins all over the body are prominent, especially those of the thorax and epigastrium. No caput medusæ. No clubbing of fingers. Capillary pulse is present. Radial pulse is eighty per minute, regular, full, and moderately hard.

Heart: No bulging at base or apex. Small area of pulsation in suprasternal notch, also in the supraclavicular fossæ. No thrills. Auscultation reveals normal heart tones throughout. No evidence of aortic aneurysm. When the patient is in a recumbent position with arms thrown above his head there is a very marked tumor-like distention of the jugular vein above on each side; also of the

superficial cervical veins. This dilatation disappears when he sits or stands.

Respiratory System. Septal spur. Throat hyperemic. Some depression of supra- and infraclavicular fossæ with atrophy of supra- and infraspinati muscles. Intercostal spaces are depressed. Ribs are prominent. Chest symmetrical. Thoracic respiration defective. Vocal fremitus increased over right chest, superiorly especially. (For results of percussion see Figs. I to IV.)

Auscultation: Breath sounds distant over areas of dulness. Few crackling rales heard at the end of inspiration over the right infra-axillary space. No bronchial breathing heard over any part of the lungs. There has been no cough or expectoration during this examination.

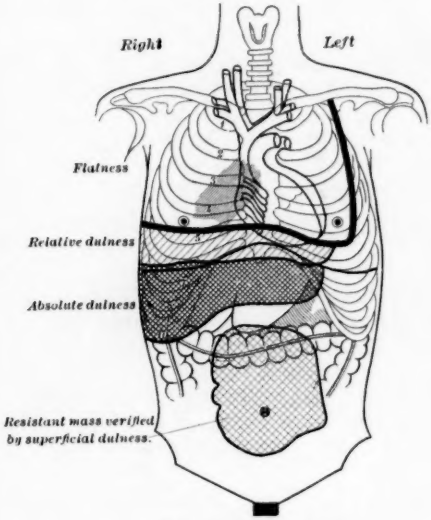

FIG. I.—Patient lying.

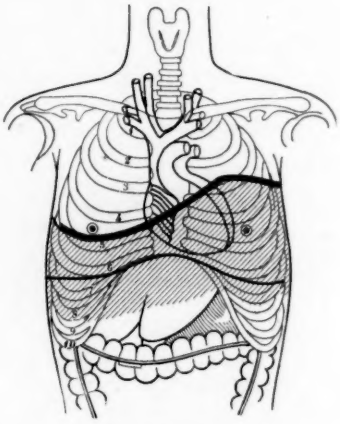

FIG. II.—Patient sitting.

Digestive System. Lips and tongue normal. Breath offensive. Gingivitis and pyorrhea present. Abdomen very prominent and symmetrical. No bulging in flanks. Umbilicus very prominent. Abdominal wall edematous. Palpation reveals a tense abdomen with a dense palpable mass of the size and shape as noted in Fig. I. This mass appears to be solid. Margins are more or less irregular. It is movable and slightly tender. Liver and spleen cannot be outlined definitely by palpation. There is a tympanitic area surrounding the tumor and the lumbar regions show dulness.

Genito-urinary System. Kidneys not palpable because of tenderness of abdomen. Bladder not distended. Penis and scrotum

markedly edematous. Prepuce edematous and cannot be retracted. Testes normal. No varicocele. Vasa not palpable.

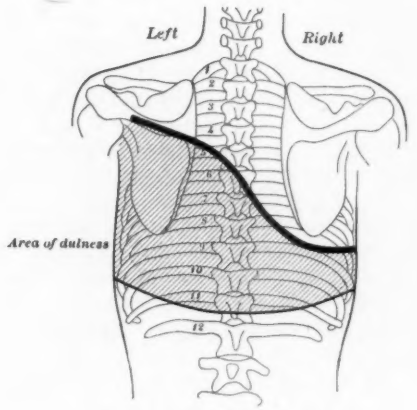

FIG.—III.—Patient sitting.

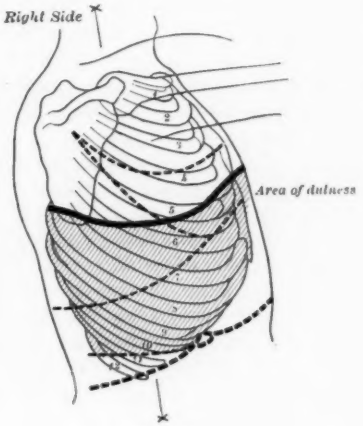

FIG. IV.

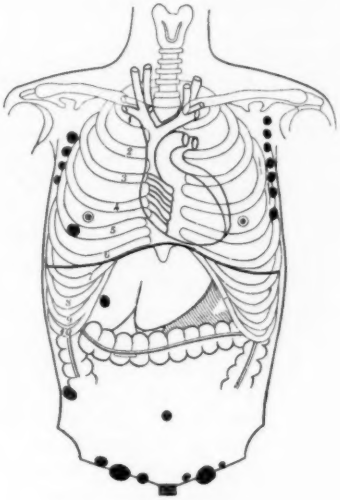

FIG. V.

Glandular System. Thyroid atrophied. Thymus not in evidence. (See Fig. V, showing enlarged lymph glands.) Epitrochlear glands each the size of a small bean. Axillary glands enlarged.

Cervical glands shotty. Salivary glands normal. The inguinal glands on both sides are greatly enlarged, there being one on the right side about the size of an English walnut and one on the left side as large as a small hen's egg. There is a chain of glands in the axilla on each side, each about the size of a filbert. There is one small gland in the region of the right nipple, one in the right lumbar region, one in the left lower quadrant, and one below the right costal margin. Femoral glands are also enlarged. Popliteal glands cannot be palpated.

Rectal Examination. No hemorrhoids. No impaction of feces. Sphincter has good tone. Prostate normal. Vault of rectum is tense and bulging. There is possibly palpable a lobulated mass.

Urinalysis: Albumin positive; sugar negative; no casts; no chyle.

Blood. Red-blood cells, 4,600,000; white-blood cells, 18,760. Hemoglobin, 85 per cent.; color index, 92. Lymphocytes: small, 55 per cent.; large, 7.5 per cent.; indentate nucleus, 1 per cent.; neutrophilic myelocytes, 1 per cent.; polymorphonuclear neutrophiles, 33 per cent.; eosinophiles, 0.5 per cent.; basophiles, 1 per cent.; unclassified, 1 per cent. In stained specimen reds seem normal.

Roentgen-ray examination by Drs. Case and Van Horn on April 6, 1914, revealed "Hydrothorax involving the right half of the chest. Level of fluid (patient standing) about the sixth rib posteriorly."

On April 8 and 21 punctures of the pleura were made and 48 and 54 ounces of fluid respectively were removed.

Dr. Moody's report on fluid: Opaque, milky, red; no odor; sp. gr., 1017. Alkaline; albumin positive; sugar negative. Urea, 0.6 per cent. Many red-blood cells. Large amount of fat.

Dr. A. J. Carlson, department of physiology, University of Chicago, reports that fluid is true chyle with the admixture of a small amount of blood.

On April 14, 1914, a gland was removed from below the right costal margin by the writer. Examination by Drs. Le Count and Moody revealed a diagnosis of small round-cell sarcoma? Lymphosarcoma or pseudoleukemia.

On April 18, 1914, a gland removed from the inguinal region by Drs. L. L. McArthur and T. J. Gunther. Diagnosis: round-cell sarcoma.

Subsequent History. On May 12, 1914, the patient left the hospital and returned to Chicago Heights, where he died September 24, 1914. Paracentesis of the chest was performed about once every two or three weeks and about 1 liter of fluid removed several times, then the amount removed was gradually decreased. An autopsy was promised, but the doctor was out of town when the patient died, and his assistant failed to obtain the postmortem.

Anatomy of Thoracic Duct. The thoracic duct extends from the second lumbar vertebra, where it originates, to the junction of

the internal jugular and left subclavian veins, where it terminates. It is the common collector of all the lymphatic vessels of the subdiaphragmatic portion of the body, and, moreover, frequently, but not invariably, receives the left jugular, subclavian, and internal mammary trunks, which bring the lymph from the left supradiaphragmatic portion of the body.

Course, direction. It is rare for the duct to arise below the second lumbar vertebra. Its origin is, however, often situated on the first lumbar or even on the twelfth dorsal. It runs at first vertically upward, passing a little to the right of the midline. Then from the sixth to the fourth dorsal it changes its direction and runs obliquely upward and to the left, in this manner crossing the anterior surface of the vertebral column in a slanting direction and continuing its ascending course as far as a horizontal line drawn through the lower border of the sixth cervical vertebra. At this point it quickly changes its direction, describes a curve with the concavity downward, and runs downward, outward, and forward and terminates in the venous junction. Its caliber varies in different parts. At its origin it has a dilated portion generally termed reservoir or cistern or pecquet (receptaculum chyli). It is in the middle part of its course that the duct is least developed, measuring only 4 to 6 mm. in diameter. At its termination there is a dilatation represented by Mascagni and called the ampulla.

PHYSIOLOGY. The physical and chemical properties of chyle vary at different times and under various circumstances; the most important factor determining its properties is, however, the character of the food in the intestinal canal. Most of the knowledge of the character and composition of chyle has been derived from experiments on the lower animals, especially the dog, in which animal it is not difficult to insert a cannula into the thoracic duct where it joins the left subclavian, at the root of the neck. Unfortunately this fluid is not pure chyle, but consists of a mixture of chyle and lymph coming from the lymphatics of the liver, kidneys, pelvis, abdominal wall, lower extremities, etc.

Chyle when a mixed diet is given is a white opaque fluid, occasionally colored slightly red or yellow from the accidental presence of red-blood corpuscles. In herbivora it may have a greenish tinge from the chlorophyl derived from the food. Reaction is alkaline, due to carbonates and phosphates of sodium. Sp. gr., 1018 to 1025. Salty taste and odor (due to volatile, fatty acids) peculiar to the animal from which it is derived. It coagulates on standing sometimes more and sometimes less readily. Microscopically it contains leukocytes and fat granules, the latter having a peculiar Brownian movement.

Chyle obtained from the lacteals before they pass through lymph glands is found to contain fewer leukocytes than that from vessels which have passed through these glands. A constant stream of

leukocytes thus passes from the chyle into the blood. This is an important source of the leukocytes of the blood.

CHEMICAL ANALYSIS (MUNK) IN MAN.

One hundred parts.	Chyle.	Lymph.
Water	92.2	95.2
Solids	7.8	4.8
Fibrin	.1	1.
Proteids	3.2	3.5
Fats, lecithin, and cholesterin	3.3	traces
Extractives	.4	.4
Salts	.8	.8

This table shows very clearly that chyle differs from ordinary lymph in but one important point, viz., in containing a larger percentage of fat.

In exceptional cases chyle contains a larger percentage of sugar than does lymph. Chyle differs from serum in two important particulars: it contains a larger percentage of fats, but a smaller percentage of proteins than does blood serum. The amount of urea in chyle is, according to Gehant and Quinquaud, greater than in the blood.

Munk and Rosenstein (to whom we are indebted for nearly all of our knowledge of the absorption of fat in man) had the opportunity of observing and experimenting upon a girl who, as a result of elephantiasis of one leg, had a fistula in the thigh which communicated through the left lumbar lymphatic duct with some of the lacteals. It was found that when fat was given to the patient two-thirds of it could be recovered from the fluid escaping from the fistula in the following twelve hours; further examination of the blood showed no more fat to be present than when the patient was fasting.

The soaps in chyle amount to 0.2 per cent. The fat in chyle is almost entirely in the form of neutral fats. The fat granules are less than 1 μ in diameter and show Brownian movement.

When large amounts of sugar are fed, some may be absorbed by the lacteals and appear in the chyle, but not so with protein. On the other hand, Asher and Barbera found that when a very large amount of protein was introduced into a dog's stomach as much as 6.4 per cent. of it could be recovered from the chyle.

Noel Paton observed the flow of lymph from the thoracic duct in a case in which the duct had been injured during an operation for sarcoma of the neck. He estimated the normal amount to be 130 to 195 c.c. per hour. His patient, however, was not in normal condition.

Munk and Rosenstein found from 70 to 120 grams of chyle escaped per hour from the fistula before and 150 grams after a meal. This was not pure chyle but a mixture of chyle and lymph.

The force exerted upon the contents of the thoracic duct by the passing current of blood in the subclavian is nothing more than an illustration of the hydraulic principle of Venturi, *i. e.*, if a stream is made to flow through a tube into which another opens and communicates at its distal end with a reservoir of water a current will be established in the second tube and will continue as long as the stream flows through the first tube or any fluid remains in the reservoir of the second. The anatomical junction of the thoracic duct with the venous system is peculiarly favorable to the maximum development of this principle, for the near affluence of the internal jugular and the downward inclination of the duct to the subclavian, contribute to enhance the effect upon the current of chyle. Out of this principle of Venturi must grow the converse, that any retardation of or obstacle to the current of blood in the subclavian vein, either from diminution of its lumen or from regurgitant heart affections, must slow the movement of the chyle in the duct and in its tributaries. Hammersfahr discusses the question of the permeability of the pleura to chyle, and concludes that the intact pleura is permeable.

Morton performed a number of experiments upon dogs by ligating the thoracic duct; in some the receptaculum and in others the lacteals burst. In every case there was extravasation of chyle.

In Sir Astley Cooper's experiments when rupture occurred it took place at the receptaculum, and Dupuytren's experiments on horses were followed by similar results. Cooper says it is not necessary to tie the duct. If the animal is fed with milk and the extremity of the duct compressed one-half hour afterward the receptaculum will rupture.

Busey quotes from Niemeyer's text-book of *Practical Medicine* as follows:

"Obstructive engorgement of the great veins extends also to the thoracic duct. When the subclavian vein is filled to distention the flow of chyle and lymph must encounter a resistance equal to that opposed to the current of any other vessel which empties into the subclavian. Nay, if lymph be the source of the fibrin of the blood we see, upon simple physical grounds, why the blood of emphysematous patients is poor in fibrin, why the venous crasis presents hyperinosis and increase of fibrin. Restricted afflux of chyle must, moreover, prejudice the nutrition both of the blood and of the entire organism. It is one of several causes which contribute to the general emaciation and to the premature marasmus of the emphysematous persons; perhaps too it may account for the lack of albumin in the serum, which produces a tendency to the establishment of dropsical symptoms."

He also quotes Hertz as follows:

"The inadequate emptying of the thoracic duct into the left subclavian vein overdistended with blood will in cases of pulmonary

emphysema lead to impoverishment of the blood insofar as concerns such elements as are derived from the lymph, the colorless blood corpuscles, fibrin and albumin."

This explains very well the fact that after one of the inguinal glands was removed from our patient there was considerable oozing of blood from the wound even on the fifth and sixth days.

Schmidt-Mulheim tied the thoracic duct of a dog in a most complete manner, securing also the cervical and both subclavian veins. On the sixth or seventh day the dog, in excellent condition, was killed and milky fluid was found around the thoracic duct and in the chest and abdomen. No rupture of the duct could be made out.

In the 47 cases collected by Baldwin the age incidence, where age was noted, was:

Under 10 years	2 cases
11–20 "	8 "
31–40 "	7 "
41–50 "	8 "
51–60 "	3 "
60+ "	2 "

The average age was thirty-six years. The greatest number occurred between eleven and fifty-one years. Of all cases of milky fluid in the chest collected up to 1900, 54 in all, 31 were chylous, 13 chyliform, and 10 doubtful. In 41 true cases in which sex was given, 31 were males and 10 females. Sale's patient was a male, as was ours.

The causes as given in 47 cases were as follows: 16 from chest injury; 9 from pressure exerted upon the duct by new growths outside the duct or by tuberculous lymph nodes; 9 from secondary growths in the duct; 4 from thrombosis of the left subclavian vein; 2 from proliferating lymphangitis; 2 from aneurysm-like dilatation of the duct; 1 from thrombosis of duct; 1 occurred during an operation for removal of carcinomatous lymph nodes of the neck; 1 was due to obstruction of the radicles of the duct from inflammatory thickenings in the mesentery; 1 from mitral disease; 1 from filaria.

Simon records a case in which a lymphangioma of the leg reached the thorax and burst into the pleura.

All of these causes produce either a break in the continuity of the endothelial lining of the duct or put the endothelial cells under such abnormal conditions that their nutrition is impaired and consequently they allow the transudation of chyle.

The symptoms of chylothorax which result directly from the condition are not characteristic. They are those of hydrothorax or pleural effusion. In most cases the chief and at times the only symptom is a gradually increasing dyspnea. In fatal cases this may be accompanied by a rapidly progressing emaciation, although the patient may have a good appetite and eat well. A few patients

complain of pain in the affected side if the condition is unilateral and of a general indefinite dull pain in the chest if bilateral. There is lagging of the affected side and more or less obliteration of the intercostal spaces. If the quantity of fluid is large there may be considerable displacement of the heart. Palpation reveals lessened or absent vocal fremitus, depending upon the amount of fluid. Percussion gives a dull note on the affected side laterally and behind, the line of dulness being higher in front and lower in back when the patient is sitting and reversed when in a recumbent position.

Edwards says 60 per cent. of cases occur on the right side.

In 17 of 47 cases there was an accompanying chylous ascites; in 1 chyluria: in 1 milky diarrhea. Bayer collected 20 cases of combined chylothorax and chylous ascites.

Edwards, in 1901, was able to collect only 2 cases of chylopericardium; 1 from leakage of chylous fluid from the pleura; the other from rupture of chyle vessels.

The diagnosis of chylothorax, as noted above, is made by paracentesis. The fluid is usually semitranslucent, milky, and opalescent, of alkaline reaction, and sp. gr. about 1020. If allowed to stand it separates into two layers: an upper, cream-like in consistence, and a lower layer watery in character. If the whole is well shaken and extracted with ether or treated with sodium or potassium hydroxide the fluid loses its milkiness and becomes clear. Chemical examination shows 90 to 99 per cent. water and 0.02 to 0.92 per cent. fat.

Sale, in 1913, reported a case of chylothorax in a man who was living and doing well six months after the condition was diagnosed and treated. The blood in his case contained 95 per cent. hemoglobin; red-blood cells, 4,900,000; white-blood cells, 4800; large polymorphonuclears, 62 per cent.; lymphocytes, 32 per cent.; mononuclears and transitionals, 4 per cent.; eosinophiles, 1 per cent.; mast cells, 1 per cent. In attempting to explain the pathology in his case he says:

"There may very well be a tumor, *e. g.*, tuberculous or luetic gland, exerting pressure on the left subclavian vessels, diminishing the pulse wave in the left radial and at the same time retarding the flow of and damming back the chyle in the thoracic duct. It may be necessary further to assume that the thoracic duct runs upward through the mediastinum to the right of the azygos vein and in close juxtaposition to the right pleura, as indeed sometimes happens."

In 1907 Dock reported a very interesting and instructive case, viz., in 1902 diagnosis of abdominal tumor was made by Prof. de Nancrède. Soon after many glands enlarged in the neck, groins, and axillæ. In 1906 the abdomen began to enlarge until the waist measured sixty inches. Great dyspnea. A grating sensation in the abdomen was audible to others as well as to the patient.

Under treatment by salines for six weeks waist measurement was reduced to thirty-six inches. The abdomen was aspirated twice and 6 and 9 quarts of pink, opaque, milky fluid were removed. One year later 6 liters of similar fluid were removed. Blood-pressure: systolic, 100 to 104; diastolic, 55 to 62. One axillary gland removed for examination.

Dr. Warthin's report: Lymphocytoma (lymphosarcoma); aleukemic stage?

Autopsy. Thoracic duct: extending from receptaculum chyli to subclavian vein is a solid cord of tissue, larger below, where it is about 4 to 6 cm. in diameter, gradually decreasing above to 2 cm., filling up the greatly dilated thoracic duct. On section it is pale with scattered reddish spots, medullary uniform consistence; very cellular, resembling the abdominal tumor and the lymph glands in all respects. Above the tumor mass projects slightly into the subclavian vein. Below the large mass in the receptaculum chyli is directly connected with the retroperitoneal and mesenteric mass of cords of similar lymphoid tissue.

Blood: white-blood cells, 625 cells counted; lymphocytes, 69.8 per cent.; large mononuclears and transitionals, 7 per cent.; polymorphonuclears, 27.4 per cent.; eosinophiles, 1.3 per cent.; basophiles, 3 per cent.; normal small lymphocytes, 1 per cent.

Sediment of ascitic and pleural fluid shows lymphocytes almost exclusively. Sternum easily fractured and red marrow hyperplastic.

Prognosis. The prognosis in many cases may be good. In those due to obstruction the anastomosis, which occurs only high in the chest, may do compensatory work and relieve the condition. Internal rupture of the thoracic duct is not always fatal. In cases due to injury to the duct from external causes proper treatment frequently brings about a cure. Handmann cites the following case:

A man had his chest caught between the drive wheel of a steam engine and a wall. He was taken to the hospital, where the left clavicle and several ribs were found to be fractured. Two days later effusion was discovered in the left pleura. Exploratory puncture yielded milky fluid of a rosy color. Chemical and microscopic examination showed the presence of chyle mixed with blood. Ten days later the red corpuscles had disappeared and the effusion had the appearance and composition of pure chyle. Absorption took place without complications and the patient recovered fairly rapidly.

Treatment. The treatment of chylothorax depends entirely upon the cause. In those cases due to chronic obstruction, aspiration, rest in bed, and nourishing food are indicated. A word of caution in regard to paracentesis: Do not remove too much at one time, because (1) of the disturbance of balance of the circulatory pressure, and (2) when the pressure exerted by the fluid is released it favors the

exudation of more fluid. Erb described a case of lymphangiectasis of the thoracic duct with chyle in the right pleural cavity in which the patient lived two months, was tapped eight times and lost twenty-five liters of chyle.

Cases due to chest injury are treated similarly. Where the cause is injury during operation, as for removal of carcinomatous or tuberculous lymph nodes in the neck, the duct may be ligated, resected, or packed.

To sum up our case, it is probable the pathology is as follows: The patient developed lymphosarcoma of the mesentery. Metastasis occurred in the inguinal, axillary, and abdominal wall lymph glands and in the thoracic duct. The tumor growing in the duct, or metastases in the mediastinal lymph glands caused obstruction, partial or total, of the duct with consequent transudation of chyle into the pleural cavities. The blood in the specimen was probably due to hemorrhage from the tumor.

CONCLUSION. In conclusion, I wish to express my appreciation of Dr. Preble's kindness in permitting me to report this interesting case, and to those whose names are mentioned in the paper, my sincere thanks.

BIBLIOGRAPHY.

Busey. AM. JOUR. MED. SC., New Series, xc, 373.
Dock. AM. JOUR. MED. SC., New Series, 1907, cxxxiv, 634.
Shaw. Jour. Path. and Bact., 1900, vi, 339
Sherman. Arch. of Ped., 1907, xxiv, 646.
Tennings and Rich. Arch. of Ped., 1907, xxv, 195.
Edwards. Ref. Hand-book Med. Sc., 1901, iii, 78.
Baldwin. Ref. Hand-book Med. Sc., 1908, p. 463.
Benedict. Ref. Hand-book Med. Sc., 1914, p. 62.
Sale. Interstate Med. Jour., 1912, xix, 50.
Herzog, Harris and Preble. Jour. Am. Med. Assn., February, 1899, p. 275.
Milton. Brit. Med. Jour., 1907, No. 2, p. 1210.
Newman. Glasgow Med. Jour., 1903, lix, 117.
Delamere, Porier and Cuneo. The Lymphatics, 1904, p. 292.
Edwards. Principles and Practice of Medicine.
Salkowski. Virchows Arch., 1909, clxxxxviii, p. 189.
Bargebuhr. Deutsch Arch. f. klinische Med., 1895, xli, 161.
Munk and Rosenstein. Virchows Arch., cxxiii, p. 230.
Lammers. Zur Kasuistik des nichtraumatischen Chylothorax, Borna, Leipzig, R. Moske, 1910.
DeLange. Nederl, Tijdschr v. Geneesk. Amst., ii, 1913, 431.
Hammesfahr. München. med. Wchnschr., 1907, lvi, 1876.
Handmann. München. med. Wchnschr., 1899, xlvi, 181.
Schmidt-Mulheim. Arch. f. Physiol., Leipzig, 1877, p. 553.
Erb. München. med. Wchnschr., 1896, Bd. xliii, p. 110.
Simon. Mitth. Grenzgeb. d. Med. und Chirg., Bd. v, H. 2.
Hasebroeck. Zeit. f. physiol. Chemie, 1888, p. 289.
Hertz. Ziemssen's Cyclop., v, p. 382.
Asher and Barbera. Centralblatt f. Physiol., 1897, xi, 403.
Morton. Donald Monroe, Essay on Dropsy and its Different Species, pp. 22 and 23.
Sir Astley Cooper. Medical Records and Researches, p. 100.
Niemeyer. Text-book of Practice of Medicine, vi, p. 120.
Noel Paton. Jour. of Physiol., ii, p. 109.
Günder. Inaug. Diss. München, 1913, Kastner and Callwey.
Dieulafoy. A Text-book of Medicine.

THE ENERGY INDEX OF THE CIRCULATORY SYSTEM.

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Various methods of estimating the work of the heart and circulatory efficiency have been proposed from time to time. Some were based upon experimental and laboratory proof, others upon clinical observations, and yet out of the many there is not one that is generally accepted as being better than the rest. All of which, I believe, goes to show that up to the present time, for clinical purposes, the problem has not been approached from a correct stand-point, and has not been solved.

Strassburger[1] believed that the pulse pressure divided by the systolic pressure indicates the vascular resistance and the work of the heart. His far-reaching conclusions, however, were opposed by Sahli.[2]

Tigerstedt[3] proposed the formula P.P.MP.R. velocity, and the P.P.MP.R. efficiency of the heart as a pump.

This formula is the same as Strassburger's, and, therefore, has the same limitations.

In 1911 Goodman and Howell,[4] following the work of Tornai[5] and of Fisher,[6] constructed a formula based upon the assumption that the first and fourth phase of the auscultatory method indicates cardiac weakness, and the second and third phase indicate cardiac strength. Their method consisted in determining the percentage relation of the C. W. phase and the C. S. phase to percentage of the pulse pressure. If the C. S. were greater than the C. W., then compensation was considered good, and *vice versa*. The method has been applied clinically and found wanting.

In 1913 Stone[7] proposed a method of estimating the heart's work. The assumption of Stone was that normally the pulse pressure constitutes 50 per cent. of the D. P., and that whenever the pulse pressure is over 50 per cent. of the D. P., then the increment represents cardiac overload.

I show here that in a series of 742 normals the P. P. may constitute anywhere from 20 per cent. to 80 per cent. of the diastolic pressure in 80 per cent. of the cases; and while the average of the figures is 50 per cent., yet it does not at all hold true that in the normal person the P. P. equals 50 per cent. of the D. P.

[1] Arch. f. klin. Med., 1905, lxxxv.
[2] Münch. med. Wchnschr., 1903, No. 47.
[3] Swan, John M., Arch. Int. Med., February 15, 1915, xv, No. 2, p. 269.
[4] Ibid. [5] Ibid. [6] Ibid.
[7] Clinical Significance of High and Low Pulse Pressure, with Special Reference to Cardiac Load and Overload, Jour. Am. Med. Assn., October 4, 1913, p. 1256.

TABLE I.—RELATION OF PULSE-PRESSURE TO DIASTOLIC PRESSURE IN SEVEN HUNDRED AND FORTY-TWO NORMAL PERSONS.[8]

5 to 10	2		
10 to 20	18		
20 to 30	68		
30 to 40	111		
40 to 50	122	249 cases	461 cases	597 cases
50 to 60	127	33%	62%	80%
60 to 70	101		
70 to 80	68		
80 to 90	55		
90 to 100	25		
100 to 110	29		
110 to 120	3		
120 to 130	3		
130 to 170	10		
Total	742		

We may note that the greatest number of cases do occur near the 50 per cent. mark, and if we were to strike an average it would be close to 50 per cent., yet this would be far from representing the actual truth. These tables show there is a wide range both above and below the 50 per cent. mark in normal individuals. Our findings here warrant only a statement that the pulse pressure equals from 20 to 80 per cent. of the diastolic pressure in about 80 per cent. of the cases. And this is where we stand today. Certainly it cannot be said that any of the above methods have withstood critical investigation. There is no known method which satisfactorily indicates the amount of work which the heart or the cardiovascular system is performing; nor when the work thrown upon the circulatory system is becoming greater than its functional capacity. Nor do we have a means of measuring accurately the total work of the circulatory system and the amount of energy expended in the performance of that work. It seems, then, that we must approach this problem by another route; and such is my present purpose.

In 1914 I[9] presented a method of estimating the activity of the cardiovascular system. The purpose of this method was to indicate the expenditure of energy by the circulatory system in the act of maintaining the circulation, and it was based upon a calculation made from the three measurable factors of the arterial circulation. I wish to emphasize the fact that in this method we are dealing only with measurable factors and not inferences, such as velocity, work of the heart, functional capacity, etc.

However much one's experience may have taught him of the condition of the circulatory system, of the degree of its activity, and of its efficiency, nevertheless the all-important clinical evidences

[8] Barach and Marks, Blood-pressures, Arch. Int. Med., April, 1914, xiii, 648–655.
[9] Barach, Joseph H., The Energy Index, Jour. Am. Med. Assn., February 14, 1914, lxxii, 525.

relative to the arterial circulation which one may record for the understanding of another are the systolic and diastolic pressures and the pulse rate.

When we go beyond these evidences in attempting to measure such activities as the blood flow, the cardiac output, functional capacity of the heart, the cardiac load, etc., we find ourselves in the realm of speculation. And while it would be highly desirable indeed to be able to make such measurements, nevertheless it has been amply proved that our present-day methods are insufficient for such purposes.

Measurable Factors in the Circulation. At the present time our clinical methods are almost entirely limited to the determination of the systolic and diastolic pressure and the pulse rate, and these observations may be made with a minimum of apparatus and technic. With the mercury manometer and by the auscultatory method we can determine the values of these three factors with certainty and accuracy.

Much has been said and written of the pulse pressure; it has been used as a basis for calculation of the blood flow, the work of the heart, cardiac load and overload, etc.; but after numerous observations of my own and a *résumé* of the work done by others, I am inclined to believe that up to the present time at least the estimation of pulse pressure has added comparatively little to our total knowledge of the circulation. I do believe that we will still gather some facts by studying the pulse pressure under certain conditions, but up to the present this has not yet been accomplished. The important factors are the systolic pressure which indicates the ventricular force, the diastolic pressure which indicates the intravascular tension during diastole, and at the same time the peripheral resistance, and the pulse rate which designates the frequency with which the heart must contract to maintain the flow of blood as required by the organism. It may be stated as an axiom that no alteration in function of the circulatory system can take place, but there is a change of values or a readjustment in more than one of the three factors. These three factors are interdependent, one upon the other, and are constantly adapting reciprocally to one another according to the needs of the organism. The relation of systolic and diastolic pressure and pulse rate, one to the other, may well be illustrated by comparison to a triangle of fixed area in which if one line of the triangle is altered the other two are likewise changed. I illustrate this by shaping a piece of cord or a chain in the form of a triangle, by which is readily seen that changing the length of the base or either one of the sides of that triangle alters the value of the other two sides.

Adaptation of Maximum and Minimum Pressures and Pulse Rate. That there is a constant adaptation of each factor in the triad to the others is shown in the following results obtained from

a series of 24 cases. These observations were made in young men previous to a race of 24.85 miles. The young men were in extraordinarily good physical condition. We found that change of posture from horizontal to erect caused an increase of pulse rate in 14, a diminution in 4 and no change in 6. The maximum pressure was diminished in 11, unchanged in 3, and increased in 10. The minimum pressure was diminished in 9, unchanged in 9, and increased in 6. After the race, in which 19 out of the 24 finished, when the blood-pressure had fallen fully 20 per cent., and the subjects were in a state of exhaustion, upon change from horizontal to erect posture the pulse rate was increased in 18 and unchanged in 1. The maximum pressure was diminished in 11, unchanged in 3, and increased in 5. The minimum pressure was diminished in 7, increased in 6, unchanged in 4, and not obtained in 2.

The conclusions from the above observations are that whether the vascular tone be of the highest attainable state of efficiency or in a state of exhaustion, each element in the triad is a constantly varying factor, and that whether the cardiovascular tone be good or poor, the manner of reaction appears to be the same, at both times being accomplished by a readjustment of all the factors. It appears, therefore, that these observations bear out the previously stated axiom.

Adaptation of the Triad in Cardiac Hypertrophy. Another example of the accommodation of these factors, one to the other, is to be found in the following figures based upon observations in a series of athletes who presented the pure form of cardiac hypertrophy—the athletic heart. In this series of cases in which we knew that the left ventricle was enlarged because of its appearance behind the fluoroscope and by physical examination, and in which the systolic pressure was increased, we found that the pulse rate was slower than in a series of subjects who had not undergone systematic physical training. Whereas, in a series of cases in which the maximum pressure ranged between 100 and 120, the average pulse rate was 79 in 29 non-trained men and 76 in 12 trained men. In a series in which the maximum pressure ranged from 130 to 140 the pulse rate was 82 in 22 non-trained men and 72 in 7 trained men.

From this we see that when the left ventricle becomes hypertrophied and the ventricular force and output are greater, the conserving forces of the body will cause a slowing of the pulse rate.

By a slowing of the pulse rate the total expenditure of energy per unit of time in the hypertrophied heart was not greater than in the non-hypertrophied heart. As measured by the S. D. R. index the average energy expenditure in the 100 to 120 non-hypertrophied cases was 15,908 mm. Hg. per minute, and in the hypertrophied cases 15,706 mm. Hg.

In the cases in which the maximum pressure ranged from 130 to

140 mm. Hg. the energy index of the non-hypertrophied cases was 17,960 mm. Hg. and 16,856 mm. Hg. in the hypertrophied cases, showing that whether the heart is hypertrophied or not, the normal organism requires but a certain fulfilment of function, and that the hypertrophy is necessary only for the occasion of greater effort. Along with the other features which this method of calculation seems to bring out, these foregoing evidences point clearly to the fact that if we are to come to a correct conclusion as to the activity of the circulatory system we must take into our calculation the complete triad.

THE S. D. R. INDEX. Since the evidences upon which we may depend are included in the triad formed by the systolic pressure, diastolic pressure, and pulse rate, it seems that a calculation based upon this triad must give us the desired information relative to the activity of the arterial circulation. Such is the purpose of the S. D. R. index.

The premise here is that each pulse beat is composed of two successive phases—the systolic phase and the diastolic phase—and that the total force exerted with both phases is what constitutes the entire beat. The systolic pressure in an artery is that amount of force exerted with the systole which is capable of lifting a column of mercury to a certain height. The diastolic pressure is the force exerted by the intravascular tension during the diastolic phase. For example, in a certain case the systolic force (kinetic energy) is equal to the lifting of 120 mm. of Hg. and the diastolic force (kinetic energy) is equal to 80 mm. of Hg. pressure. Therefore, with one pulse beat the measurable quantity of force (kinetic energy) is equal to the lifting of 200 mm. Hg., and with 72 such pulse beats the force would be 72×200 or 14,400 mm. Hg.

For clinical interpretation we may presume that the systolic pressure represents the effort of the arterial system, and the pulse rate represents the effort of the heart, as a whole, to maintain the circulation. Or we may assume that we are simply trying to determine the degree of effort expended by the circulatory system in carrying on the circulation to maintain the needs of the organism. For that purpose we note the energy of the systole, of the diastole, and how many times per minute that much energy is expended. We do not deal here with absolute results, the product of our calculation does not quantitatively measure, but it does indicate clearly the expenditure of energy per unit of time.

THE NORMAL S. D. R. INDEX. If we are to use this method of estimating the energy expenditure per unit of time we must establish the values of normal persons. For that purpose the following table has been constructed. This table is based upon 250 normal individuals in whom the pressure ranged within what we consider the extremes of normal limits. Here are included only those cases in which the minimum pressure did not exceed 100 mm. Hg. and

the pulse rate did not exceed 90 beats per minute. With an upper limit of about 150 mm. Hg., I believe we are within the normal bounds.

TABLE II.—TOTAL ENERGY INDEX IN TWO HUNDRED AND FIFTY NORMAL PERSONS.

100		3 cases	average	13541	mm. Hg.	per minute
100 to 120	42	"	"	15918	"	"
120 to 130	123	"	"	16902	"	"
130 to 140	44	"	"	17690	"	"
140 to 150	22	"	"	18527	"	"
150 to 160	16	"	"	21076	"	"
	250					

I therefore believe that in normal persons, as estimated by the energy index, that the pressure does not exceed 20,000 mm. Hg. per minute.

VARIATIONS IN ENERGY EXPENDITURE AS DETECTED BY THE INDEX. Here it is my purpose to show that the maximum pressure reading alone conveys practically no information concerning the activity of the circulation.

The following table is based upon observations made upon a group of 289 young men between the ages of fifteen and thirty years. I have chosen the extreme cases of each group, and show that while Case A and Case Z both had the same maximum arterial pressures, the total energy expenditures at the time of examination was very much greater in Case Z than in Case A. This difference of activity in the circulation of these cases was quite obvious. Some of these young men entered the examination room anxious-looking, pale, with apex impact prominent, and at first glance it could be seen they were in a state of mental and nervous excitation with the usual effects upon the cardiovascular system.

The energy index in these cases showed this increased action, whereas the maximum pressure reading indicated nothing of what was actually going on at that time.

TABLE III.—TABLE OF TOTAL ENERGY INDEX IN TWO HUNDRED AND EIGHTY-NINE CASES.

Group.	No. of cases.	Maximum blood pressure, mm. Hg.	Extreme instances. Case.	Maximum.	Minimum.	Pulse.	Energy index, mm. Hg. per min.
1	41	From 110 to 120	A	115	52	72	12,024
			Z	110	88	124	24,552
2	99	120 to 130	A	124	68	68	13,056
			Z	125	100	120	27,120
3	76	130 to 140	A	138	90	64	14,592
			Z	132	118	132	33,000
4	43	140 to 150	A	142	85	60	15,436
			Z	148	98	120	29,520
5	26	150 to 160	A	150	90	76	18,240
			Z	150	115	88	27,440
6	4	160 to 170	A	164	110	68	18,632
			Z	162	80	120	29,040

EFFECT OF PHYSICAL EXERTION AS INDICATED BY THE S. D. R. INDEX. During the past year, with the assistance of Dr. W. L. Marks, of the Carnegie Institute of Technology, I made a rather extensive series of observations upon the effect of graduated amounts of physical exertion upon the circulatory system and calculated the results by the S. D. R. index. This work will be published later in detail, but for the present purpose I cite an instance of the results obtained. The exercise consisted of running to the time of a metronome at the rate of 152 steps per minute for a period of one minute:

	CASE A.				CASE B.			
	Pulse.	Systolic.	Diastolic.	Index, mm. Hg.	Pulse.	Spstolic.	Diastolic.	Index, mm. Hg.
Before . . .	72	104	78	13,104	100	120	85	20,500
15 seconds after	92	132	90	20,424	132	165	95	34,320
5 minutes after	80	120	80	16,000	108	130	90	23,760

These figures in all cases show (1) that each one of the triad is a constantly varying factor; (2) they show that with the exertion there came an increased demand upon the circulatory system, and that as this demand ceased the activity lessened and returned toward the normal, sooner in some cases than in others, and finally the figures show the degree of reaction on the part of the circulatory system.

By observing the effects of definite amounts of physical exertion upon the circulatory system, as indicated by the S. D. R. index, and by noting the degree and duration of the increase, we have come upon a method of estimating the circulatory efficiency of our subjects. This we will treat fully in a later consideration of this subject.

SUMMARY. 1. It is an axiom that changes in the activity of the circulatory system are accomplished by the adjustment of three factors: the maximum pressure, minimum pressure, and pulse rate.

2. That since these are measurable factors a calculation based upon this triad should indicate the total energy expenditure of the circulatory system.

3. The product of such a calculation, which I termed the energy index, under normal conditions represents a kinetic force per minute equal to not over 20,000 mm. Hg. pressure.

4. In the S. D. R. index or the energy index we have a method which is based upon the three measurable factors of the circulation, and one which indicates per unit of time the total expenditure of energy by the circulatory system in the performance of its functions.

THE BLOOD-PRESSURE IN PNEUMONIA.

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From a clinical stand-point the mode of death in pneumonia is of the greatest importance. On this determination the prognosis and treatment must necessarily in greater part depend. It is safe to say that the larger number of clinicians will accept the statement of von Jürgenson that, "Patients who die of pneumonia are killed by cardiac insufficiency."

The factors assigned in producing the cardiac failure are (1) the pneumonic exudate interfering with and obstructing the pulmonary circulation, thus increasing the work of the right heart; (2) the pneumonic changes in and about the lung resulting in a disturbance of the normal pulmonary influence in maintaining the circulation and (3) the injurious effects of the fever on the heart.

One of the important problems in the study of pneumonia is that associated with the causative factors of the cardiac failure.

The slight mechanical influence on the lesser circulation and the interference of the respiratory assistance to the circulation can hardly be seriously considered, especially when a small localized consolidation produces a fatal outcome or an enormous, perhaps, complete involvement of one entire lung, goes on to a favorable termination. Even the myocardial degeneration described by von Jürgenson, Zenker, and Liebermeister as due to the pyrexia was brought into question by Aufrecht when he directed attention to cardiac failure in pneumonia with slight fever and the infrequent occurrence of the same in diseases with long-protracted fever, as in typhoid.

However, it must be admitted that pneumonia patients die and the fatal termination is usually manifest by signs and symptoms of circulatory failure. At present it is generally admitted that the circulatory disturbance is produced by the pneumococcal toxemia, but how or in what manner has not been definitely determined.

Admitting that the fatal issue is brought about by a circulatory failure, the result of the toxemia, it is evident that some portion of the cardiovascular apparatus must be involved. For practical purposes this means anatomical or functional changes in either the heart or the vascular system, including the contained blood, while, undoubtedly, in some instances there is a simultaneous involvement of the entire circulatory apparatus.

Regardless of a few exceptions, it was formerly quite generally accepted that the myocardium was at fault, until Romberg[1] and his

[1] Experimentelle Untersuchungen über die Allgemeine Pathologie der Kreislaufstorung bei Acuten Infectionskrankheiten, Arch. f. klin. Med., 1899, lxiv, 652.

associates investigated the problem experimentally and arrived at the conclusion that the circulatory failure invariably followed an exhaustion or paralysis of the vasomotor center in the medulla. Since that time up to recently the vasomotor theory has held full sway, to the complete exclusion of the previously accepted idea of myocardial degeneration.

However, as might be expected, recent experimental and clinical investigation has again emphasized the importance of the cardiac involvement and with a corresponding diminution of the influence of the vasomotor mechanism.

Newburgh and Minot,[2] in their clinical study of pneumonia, among other findings, arrived at the conclusion that the blood-pressure curve did not suggest a failure of the vasomotor center. This conclusion has been amply confirmed experimentally by W. T. Porter and L. H. and I. Newburgh.[3] They were able to demonstrate that the vasomotor center was not impaired in fatal pneumonia.

Even more convincing are the microscopic findings of Willson,[4] as determined in the fatal pneumonias. In every instance he was able to detect myocardial changes due either to a toxemia or a local infection. That it could be otherwise is hardly to be expected, when it is recalled that fatal pneumonia is accompanied by a toxemia and practically every case with a pneumococcal septicemia.

With the evidence at hand it is apparent that no definite and final statement can be made, further than fatal pneumonias die with the clinical manifestations of a circulatory failure, the result of a pneumococcal toxemia and septicemia; but whether the myocardium or the vasomotor apparatus is chiefly involved remains in doubt. Perhaps it may be ultimately determined that there are various groups in which one or the other predominates, while in some, both the myocardium and vasomotor system are concerned.

On the experimental findings of Romberg and his associates,[5] G. A. Gibson[6] formulated a statement in reference to the relation of the blood-pressure to the pulse-rate, known as the Gibson rule, which is as follows: "When the arterial pressure, expressed in millimeters of mercury, does not fall below the pulse-rate, expressed in beats per minute, the fact may be taken as of excellent augury, while the converse is equally true. From the work of the last few years in my own wards no fact is more certain than this."

During the past few months a careful clinical study of the application of this rule has been made of the pneumonias admitted to the Ward Eight Medical Service at the County Hospital. In each

[2] The Blood-pressure in Pneumonia, Arch. Int. Med., 1914, xiv, 48.

[3] The State of the Vasomotor Apparatus in Pneumonia, Am. Jour. Physiol., 1914, xxxv.

[4] The Heart in the Pneumonias, Jour. Am. Med. Assn., 1914, lxiii, 981.

[5] Loc. cit.

[6] Some Lessons from the Study of the Arterial Pressure, Edinburgh Med. Jour., 1908, n. s., xxiii, 17.

instance a careful record was made of the pulse, temperature, and respiration rate every four hours. The systolic blood-pressure, by the auscultatory method, was determined at least every twelve

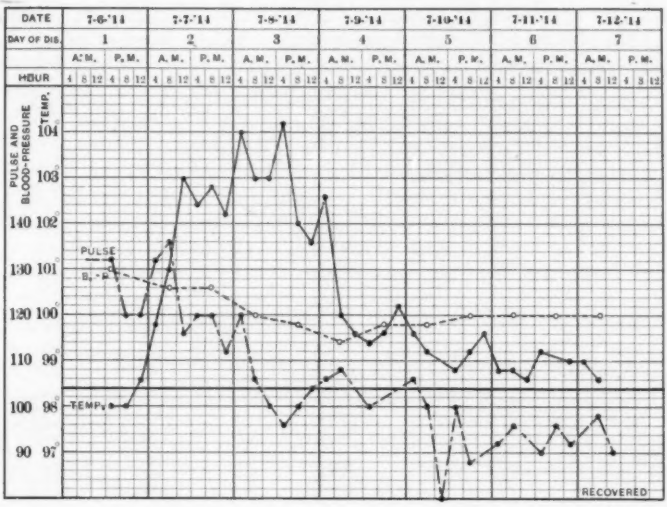

CHART I.—Chart from a case of pneumonia with recovery, showing blood-pressure well above pulse-rate.

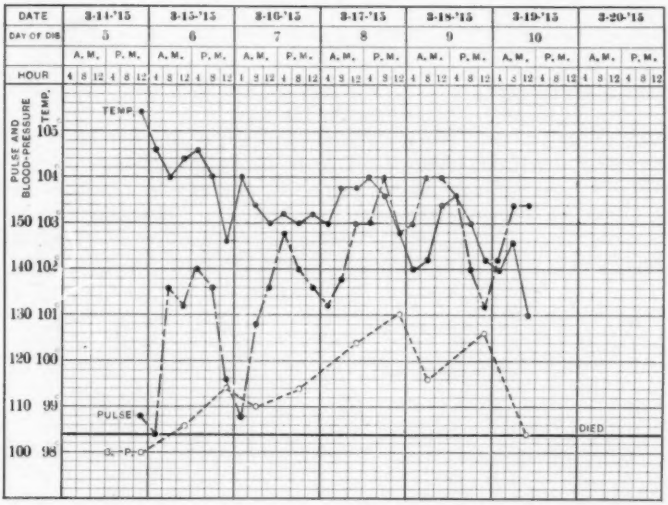

CHART II.—Chart from a fatal case of pneumonia in which blood-pressure fell far below pulse-rate.

hours. From these records a chart was made showing the pulse-rate and blood-pressure curves. For convenience the temperature curve as well as the time and amount of digitalis administered, were also included. The number of pneumonias so charted includes 31 cases, which may be divided, for further study, into two groups according to the relative position of the blood-pressure above or below the pulse-rate.

GROUP 1—BLOOD-PRESSURE CONSTANTLY, OR IN GREATER PART, ABOVE THE PULSE-RATE.

No.	Name.	Age.	Involvement.	Leukocytes.	Day of illness.	Complications.	Result.	Gibson rule.
1	M. M.	39	Left lower	14,000	4	Mitral insufficiency Nephritis	Died	Negative.
2	O. E.	44	Right lower	8,128	4	Mitral insufficiency	Recovered	Positive.
3	D. N.	39	Left lower	...	3	....	Recovered	Positive.
4	M. G.	29	Left lower	19,350	2	....	Recovered	Positive.
5	M. R.	44	Right upper	19,400	4	Mitral insufficiency	Recovered	Positive.
6	M. M.	24	Right lower	14,000	?	....	Recovered	Positive.
7	F. S.	63	Both lower	24,000	7	Myocarditis Nephritis	Died	Negative
8	E. C.	48	Left lower and upper	29,300	6	....	Recovered	Positive.
9	V. C.	27	Right lower	11,700	1	....	Recovered	Positive.
10	T. T.	23	Left lower	14,000	7	....	Recovered	Positive.
11	S. G.	58	Left lower	80,000	3	Myocarditis Obesity	Died	Negative.
12	V. M.	21	Both lower	20,000	4	Pleurisy	Recovered	Positive.
13	A. McD.	48	Right lower and middle	14,000	5	Nephritis	Recovered	Positive.
14	M. M.	56	Left lower (complete) Left upper (partial)	33,800	?	Pleurisy Dilated heart	Died	Negative
15	H. E.	70	Right lower	31,300	6	Nephritis Myocarditis	Died	Negative.
16	M. E.	43	Right lower	17,700	5	Bilateral pleurisy	Recovered	Positive.
17	E. C.	64	Left upper	27,800	6	....	Recovered	Positive.

Summary: Of the 17 cases, 12 complied with the rule, or 70.5 per cent.

GROUP 2—BLOOD-PRESSURE CONSTANTLY, OR IN GREATER PART, BELOW THE PULSE-RATE.

No.	Name.	Age.	Involvement.	Leukocytes.	Day of illness.	Complications.	Result.	Gibson rule.
1	J. K.	38	Right lower and right upper	...	5	....	Recovered	Negative.
2	T. W.	49	Left lower	20,500	7	Nephritis	Died	Positive.
3	L. S.	19	Both lower	15,000	8	Pleurisy	Recovered	Negative.
4	M. L.	61	Both left and right upper	14,250	?	....	Died	Positive.
5	A. M. R.	41	Right upper and middle	26,250	8	....	Died	Positive.
6	L. L.	13	Right upper	37,550	3	....	Recovered	Negative.
7	M. V.	35	Right lower and middle	11,700	9	Nephritis	Died	Positive.
8	N. W.	42	Right lower	16,500	8	....	Died	Positive.
9	E. D.	18	Left lower and right empyema	11,300	5	Empyema	Recovered	Negative.
10	J. S.	56	Left lower	11,800	1	....	Died	Positive.
11	G. C.	22	Left lower	36,000	6	Pleurisy	Recovered	Negative.
12	D. A.	32	Both lower	16,400	6	Pregnant (5 months) Nephritis	Died	Positive.
13	C. B.	26	Right lower	12,600	7	Pleurisy	Recovered	Negative.
14	A. D.	28	Both lower	15,100	5	....	Died	Positive.

Summary: Of the 14 cases, 8 complied with the rule, or 57.1 per cent.

As will be observed in the first group of 17 cases, 12, or 70.5 per cent., complied with the rule, while in the second group of 14 cases, 8, or 57.1 per cent., were positive, thus agreeing with the rule. Of the total of the two groups, 31 cases, 20, or 64.5 per cent., verified the observations of Gibson.

A reasonable explanation for four of the five discrepancies in the first group is to be found in the presence of a nephritis in three and a myocarditis and obesity in the fourth.

In the second group, of the 6 deviations from the rule, 3 were comparatively young, with soft elastic vessels, in which presumably a relatively lower pressure existed before the onset of the pneumonia, or, at least, were able to withstand a greater depression of the circulation.

Excluding the 7 cases in which a reasonable exception existed, of the remaining 24 only 4 failed to comply with the rule.

Aside from the prognostic significance, the blood-pressure and pulse ratio have been of the greatest assistance and satisfaction as a guide to the administration of cardiac stimulants. In some no stimulation was used, while in others one or two intravenous injections of digitalis were sufficient to reduce the pulse-rate, increase the blood-pressure, and produce a crossing of the curves.

REGENERATION OF BONE.[1]

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The regeneration of bone, formerly with reference to the repair of fractures and in the past century to the ultimate fate of the bone transplant, has been a much-debated topic. One of the earliest and foremost investigators in this field of research was the French naturalist Duhamel du Monceau, who, in 1739, called attention to the active role played by the periosteum in the regeneration of bone. But the exhaustive work of the eminent French surgeon Dupuytren, placed the subject upon a scientific basis. Ollier, Barth, Axhausen, and others have presented many valuable contributions to the subject.

Cellular Dynamics. Some idea of cellular dynamics is essential for an adequate understanding of the physiological mechanism of

[1] This article does not refer to the transplantation of compact bone into cancellous bone.

transplanted tissue. The mere removal of a living cellular mass from its regulated supply of assimilative material—the constituents of the blood and lymph—does not mean death to its individual cells. Cellular life may proceed within certain limits without either organic or somatic influence and under proper chemicophysiological environment will retain its inherent vitality long after its enforced separation from living matter. Upon these fundamental physiological factors depend the eventual outcome of all transplanted tissue, bone included. The successful transplantation of tissue is dependent upon the continuance of the cellular life of the transplant, and likewise necessitates the growth of the individual elements or their regeneration. The living cell just before its removal from the donor is undergoing katabiotic and bioplastic activities respectively, dissipation of kinetic energy in the performance of function, and the conversion of kinetic energy into potential energy, *i. e.*, storing up energy in the formation of the complex molecules of the cells—substance growth. We can dismiss the katabiotic activity going on in the cell by merely stating, for lucidity, that these activities are the responses to external stimuli, either "directly or through the intermediation of the nervous system." The length of time the transplanted cell shall continue to functionate will depend upon the amount of potential energy that it carries with it. Highly differentiated cells will have reserved a minimum of potential energy, *i. e.*, the functional demand placed upon the bone cell is so great and hence its bioplastic activity so limited that even in the most favorable environment it (bone cell) could not be expected to regenerate sufficiently to maintain the unity of the graft. Therefore, since the vegetative potentiality of the bone cell is *nil*, the regeneration of the bone must come from a more embryonic cell. "The more we study the differentiated tissues of the body the more it is brought home to us that the fully developed and differentiated cell, as such, exhibits little active multiplication, and that to a very large extent, under normal conditions, the removal of the cell worn out by use is brought about by the presence and reproductive activity of 'mother cells,' of cells, that is, present in the tissues in a relatively undifferentiated form, or, as we are accustomed to term it, of embryonic type." (Adami.) The embryonic type of bone cell is the osteoblast which is everywhere present in true osseous tissue, in great numbers, in the compact periosseous layer, in the Haversian system, the marrow, and endosteal layer. In these cells, growth is at its maximum, function at a minimum; assimilation and growth with only slight functional demands are the distinctive features of their existence. The amount of reserved potential energy of any individual cell is extremely variable, but upon its reserve capacity depends the time limit of existence before new pabulum is supplied. With the establishment of a blood supply compatible with the demands

of the graft, from a few hours to many days after the transplantation, the cells are in a more favorable condition for growth than when first transplanted. When existing upon their own reserve store of energy the cells gradually fall below the limit of maximum efficiency, so that as revascularization proceeds the cells are in active demand for new pabulum, stimulation to growth—or, as Weigert states it, "the katabiotic use of material in function removes the obstruction to growth." While the bone cells in the periphery of the graft have sufficient reserve force to maintain their vitality until reënforced by the permeation of the serum of the host, the bone cell encased in its calcified matrix at any distance from the new supply of food will become necrotic along with its ground substance. This calcium saturated ground substance must undergo dissolution before new bone can be laid down, and most likely the dissolved calcium salts are reprecipitated again by the rapidly maturing osteoblasts.

The graft consists of a multicellular mass, each cellular constituent composed of masses of biophores. The magnitude of growth of each unit mass of biophores is determined by two factors: (1) the relation of the area of surface contact of the unit mass of biophores to the intermediate substance (the cytoplasm), and (2) the relation of surface contact of the cytoplasmic mass to the surrounding assimilative material (plasma of the host). There exists a certain ratio between the optimum efficiency of the cells and their surface contact. Not until this maximum ratio is exceeded will there be nuclear division. It is readily conceived that the above relations vary for almost each individual cell of the transplant, since some cells will be more remote from the maximum supply of pabulum than others, and therefore changes in the biophores dominating the cells. Modification of the environment of like biophores, and eventually adaption of these biophores to this environment, constitutes the process of differentiation of the cells; differentiated osteoblasts are mature bone cells. Any gross change in the biophoric material is associated with corresponding alteration in the cytoplasm, histological and physiological modification of the entire cell.

Complexity of Bony Structure. The regeneration of bone is a very complex process. Bone is a tissue containing several important constituents, *i. e.*, the mature bone cell encased in a calcium salt deposit over which it rules; a complex Haversian system containing endothelium, fibroblasts, osteal fibroblasts in all stages of development, lymph spaces, and all the elements of circulating blood. Its matrix is a highly specialized ground substance which is capable of supersaturation with the earthy salts. Its many modes of development only serve to mystify the ultimate structure; probably no tissue in the human body has as many modes of development as bone. The complexity of the structure

and development is the one obstacle encountered in the solution of any problem in which bone either alone or in combination with other tissues is involved. In the study of any problem or problems in which bone receives consideration, it is of paramount importance to keep in mind the presence of the osteoblast, which cannot be differentiated morphologically from the ordinary fibroblast, but which can assume the property of either secreting osseomucin or chondromucin, and eventually becoming, during its course of development, a highly differentiated bone cell, surrounded in its mature state by calcareous walls. By virtue of its inherent power, it is the ruler of calcium deposition within the area of its influence, and also retains the power of dispersing it. In the absence of any data, up to the present writing, to the contrary, the mature bone cell is an end-product, incapable of reproducing itself, and in the event of its death the calcareous ground substance, over which its ruling influence prevades, remains "inherently immutable," requiring time and foreign-body giant cells for its removal. Although it is possible to produce division by mitosis of the mature bone cell by incubating *in vitro* on artificial media, this must not be interpreted as being possible to produce new bone. Mitosis is not always synonymous with growth.

Development of Bone. In the consideration of the problems of regeneration of bone, it is advisable at this point to merely call attention to the many modes of regeneration and development of bone. In the embryonic state, it may arise either direct from fibrous tissue, in which case it is known as intramembranous bone, or it may develop from cartilage, as an intermediate stage, and is then known as intracartilaginous or endochondral bone. It is never of primary formation, although always derived from mesenchyme. Either method is complex in its development. After it has passed through the developmental stage and true bone is formed, the process of regeneration and repair are far from simple processes. In the repair of fractures, new bone may be formed direct or formed by passing through an intermediate stage of cartilage but eventually, however formed, fills in the space between the fragments. Loss in bony structure, however produced, may demand regeneration of bone for the preservation of the function of the part. This process will vary, depending upon the type of bone upon which such a demand is placed. The space may be filled in by bone formed from the periosteum or from osseous tissue *per se*. Either process will vary with membraniform bone or chondriform bone, while in the latter type of regeneration the cartilage cells may be (*a*) converted into bone cells and the surrounding matrix converted into osseous tissue, or (*b*) through the agency of fibroblasts, layers of young cells are deposited upon the cartilaginous remains. Just what role the marrow plays in the regeneration of bone is a much-disputed topic at present.

THE METAPLASTIC THEORY OF BONE FORMATION. True bone formation in vessel walls, etc.: In this connection, it may be well to pause and inquire into the mode of formation of true bone in heterotopic tissues, such as bloodvessels, the choroid coat of the eye, and in the ossification of laryngeal and tracheal cartilage in advancing age.

For many years the formation of bone in heterotopic tissues was considered a rare incidence. But since the work of Barth (1895), Pollack (1901), Sacerdotti and Frattin (1902), Poscharissky (1905), Bunting (1906), and Brueger and Oppenheim (1908), the formation of true bone, even with its associated cellular marrow (red), is not an uncommon occurrence. W. Harvey (1907), of Toronto, was able to produce true bone in the aorta of rabbits by the application of irritants to the vessel walls. In from two to six months after the application of a 3 per cent. solution of silver nitrate or a 2 per cent. solution of copper sulphate to the outer coat of the vessel wall of the aorta, Harvey was able to demonstrate the formation of bone with its Haversian canals, with bone marrow or bone alone, or the development of osteoid tissue in areas of calcification. A very important question naturally arises as to the mode of development of bone in these unnatural situations. The metastasis or displacement theory of Cohnheim assumes the presence, in these unexpected situations, of misplaced embryonic tissue, which by some unknown force takes on active vegetative development. This theory might be acceptable if it were not for the comparatively common occurrence of such bony tissue, and moreover, the incidence points to a preponderance of such a frequency of occurrence of the process in advanced arteriosclerosis. Pollack found true bone formation adjacent to the calcium deposits in 43 out of 47 cases in which the process was studied. There are two views (Bunting) concerning the formation of bone in heterotopic tissues, *i. e.*, (*a*) that there is a direct metaplasia of connective tissue into bone after the manner of callus formation, and (*b*) that the calcific material is eroded with the formation of vascularized spaces containing tissue cells, some of which take on the function of the osteoblasts and lay down bone, some of the osteoblasts becoming included and forming the bone cell. Quoting from Bunting: "It seems clear, then, that one has here a metaplasia of connective-tissue cells into osteoblasts, for in vessels and heart valves there can be no possibility of periosteal or perichondral sprouts playing a part except in pulmonary foci. As to the stimulus which leads to this metaplasia there seems to be a uniformity of opinion, as might be expected, from the similarity of pictures presented by the different cases." Paul describes the process as consisting of three stages, as follows: (*a*) calcareous degeneration, (*b*) irritation about these areas of degeneration from fracture or other injury leading to inflammatory proliferation, (*c*) ossification in this young proliferating tissue.

Bone has always formed where young connective tissue is adjacent to calcium deposits and the metaplastic process is evidently a result of the chemical stimulus of the calcium salts. Bone cells, marrow cells, and connective-tissue cells are all developed from the undifferentiated mesoblastic cells, but in "adult life they seem to have diverged widely in nature and function." The specialized differentiation of a fibroblast into an osteoblast is a short step, and is dependent upon the nature of the intercellular substance deposited.

To return to the first appearance of true bone in the embryo, it is readily seen that highly differentiated osseous tissue is developed by a process of physiological metaplasia from the primary mesoblastic tissue, mesenchyme accompanied by a deposition of calcium salts. We must not forget that metaplasia is a constant process in the living body, occurring both as a physiological and pathological process, as is seen in the conversion of cartilage into bone and ordinary connective tissue into fat cells.

Indirect Regeneration of Mature Bone Cells. By the regeneration of any tissue is meant the reproduction of that tissue. The ultimate tissue may be produced in either one of two ways, *i. e.*, (*a*) through a process of direct regeneration (*e. g.*, epithelial cell from epithelial cell), or (*b*) by indirect regeneration (*e. g.*, erythrocytes from the mother-cell mononuclear of the marrow, etc.). A bone cell being an end-product cannot regenerate itself but must depend for its constant reproduction upon the indirect regeneration of the osteal fibroblasts with the ultimate formation of true bone cells. This process of indirect regeneration has been the stumbling-block of many researches in this field of experimentation. What is meant when regeneration of bone from bone is referred to? Certainly, regeneration of osseous tissue from osseous tissue does not refer to the reproduction of bone cells by mitosis with the formation of new bone cells and new ground substance with its deposited earthy salts. As far as the direct division of mature bone cells there is no available data, nor even a suggestion at the present time that such a division is possible in the human body. Therefore, any formation of new osseous tissue from osseous tissue must be by the indirect regeneration and development of its osteal fibroblasts into new-formed mature bone cells. Should a bone cell die through a deficiency of its inherent internal assimilation or a deficient supply of pabulum, as may happen in a transplant, the surrounding calcareous matrix over which the bone cell predominates does not undergo constant replacement and absorption, as any living tissue must, but remains unchangeable only to be removed in due course of time by the endothelial leukocytes, osteoclasts, etc. Therefore any new bone that is deposited, as in the case of the transplant, must be derived from the indirect regeneration of the osteal fibroblasts either of the transplant itself or from

the host. This does not mean that all transplanted bone dies and that all new bone is laid down by the indirect regeneration of the osteal fibroblasts. Some bone cells are capable of retaining their inherent vitality and internal assimilation and reign supreme over their stipulated area of calcified matrix. However, it must be admitted, whether by analogy or by direct proof, that the entire quota of constituents of any transplant will not live, cannot live—while other constituents, more favorably situated, will be bathed with the necessary pabulum compatible with the retention of its inherent vitality.

Specificity of the Osteoblast. As to the specificity of the osteoblast, it will suffice to say that from the present animal experimentations its specificity is extremely doubtful. Should this view prove erroneous, then it must be considered as a wandering cell in the blood stream, which with our present histological technic cannot be identified as such. The theory of the metaplastic formation of bone, as in the walls of the bloodvessels, has much in its favor.

Bone a Living Tissue. Moreover, bone is a living tissue and not an end-product, as is generally considered. It undergoes both progressive and retrogressive metabolism throughout its life, exactly like any other tissue in the human body. Old bone is continuously resorbed and new bone laid down. Bone stores up calcium, to be drawn upon in time of need just as subcutaneous tissue stores up fat and the liver stores up glycogen.

Any tissue must undergo internal metabolic changes associated with constant renewal, absorption, and repair from the time of its inception as an entity until complete cessation of its activities. These properties seem comparatively simple when tissue, soft and cellular, undergoing direct regeneration, is under consideration, but when a tissue is apparently immutable because of its hard texture and its regeneration being dependent upon the indirect development of a mother cell the complexity of the process, at first sight, is immeasurable. The mechanical resistance of the hard, calcified matrix merely delays the process of interchange between its constituents and is only a matter of time, all processes of intercellular exchange taking place as in any cellular structure in the animated kingdom. Nails and wire used in the treatment of fractures, etc., produces localized absorption of the bone until the equalization of pressure is compatible with the vitality of the part. This process of absorption of bone under very limited pressure is seen in erosion of the ribs and sternum in an aneurysm of the aorta. Osseous tissue is very susceptible to perverted metabolic processes, as is seen in the pathological changes as a result of rickets, syphilis, tuberculosis, and osteomalacia.

Growth of Bone. It will be of some advantage, now, to consider the process or processes of the growth of bone both longitudinally and peripherally. Primarily, the growth of bone is dependent upon

the internal secretion of both the pineal and thyroid glands, as is seen in cretinism, gigantism, and acromegaly. Disturbance in the secretion of the pituitary gland has been suggested as an important factor in the lamellar growth seen in osteitis deformans. McCord has definitely proved by feeding pineal gland to young animals, that in some manner it exerts a marked influence on developing bone. Feeding pituitary extract to fracture cases does not influence the time of permanent callous formation nor complete union of the fractured fragments, as has been shown experimentally.

The longitudinal growth of bone takes place at the metaphysis, *i. e.*, the diaphyseal side of the epiphyseal cartilage. In this situation, because of its nature and construction, the osteoblasts receive an abundance of pabulum for the continuance of their vegetative existence and also sufficient space for their proliferation, free from unnecessary crowding of the ultimate individual constituents. The growth of bone in this region is dependent upon the ossifying cartilage, which initiates the process and contains a full quota of all the elements necessary to its future development. If for any reason the cartilage at the epiphysis should undergo a destructive process with the complete elimination of this type of tissue, then epiphyseal proliferation would no longer be possible or at least would be retarded. Under normal conditions the growth of the bone is limited to the metaphysis; however, should the same conditions prevail in any portion of the diaphysis, the osteoblasts in this area would be stimulated to increased vegetative activity with their resultant specialized ground substance and the formation eventually of bone. These conditions are present when a limited length of the entire circumference of the shaft of a bone is removed. The gap will eventually be filled in by the proliferation of the osteoblasts in this region, both from the ends of the bones and from the periosseous layer of osteogenetic cells. Moreover, there will be renewed activity at the metaphysis with the formation of bone pushing the entire shaft toward the defect.

Bone is increased peripherally by subperiosteal osseous new formation, from the activity of the periosseous osteogenetic layer of the compact bone. This view is accepted by all during the period of development, but is contested during adult life.

Brief Résumé of the Literature. While it may seem a repetition of past publications to attempt even a brief *résumé* of the literature, since an attempt has been made to give due attention in a number of recent contributions on the subject, nevertheless the interpretation placed upon each set of experiments and conclusions varies both with the individual's fitness, either merely as a scientist or as a clinician, and with the subject matter under consideration. I shall attempt to limit my *résumé* of each investigator's researches to the statements and conclusions, specifically referring to the regeneration of bone *per se*. No attempt will be

made to discuss pro or con the conclusions, but rather to allow each individual, unbiased, to formulate his own deductions.

Axhausen (1907–1909): "The chief source of new bone which replaces the necrotic bone of the transplant is the periosteum, then next in order comes the marrow and endosteum, and third, only in case of implantation into bone defects, the osteogenetic tissues of the implantation site."

Tomita (1908) concludes that new growth of bone comes from the inner layer of cells of the periosteum and from the marrow cells. The cells of the bone itself has no power to form new bone.

Wieder (1908): "In the regeneration of bone all the various elements, viz., periosteum, cortex, endosteum, and marrow, assist in the process." "Cortical bone-forming activity does not manifest itself until after considerable absorption of the cortex has occurred, so that it may be due to the liberation of bone cells which take on new activity and again precipitate the liberated calcium salts in new situations; or it may be due to the opportunity for the ingrowth of endosteum into the widened spaces." "The deeper layers of the periosteum, the endosteum, the tissues lining the Haversian canals, and the bone cells are probably all related or identical tissues exhibiting different activities, because existing under different physical conditions."

Baschkirzew and Petrow (1912): "There remains nothing else possible than to accept the view that the chief source of the regeneration of bone transplanted into soft parts lies in the primary layer of granulation tissue which surrounds the transplant. Bone in different degrees of necrosis seems to exert a specific irritation upon the connective tissue. Bone freed from the periosteum transplanted into soft parts proves themselves capable of regeneration; periosteum is as little necessary as the marrow."

Cotton and Loder (1913): "The essential picture is summarized as follows: Disappearance of the bone cells in the trabeculæ of the transplant and also to some distance in the host. The graft is covered by a layer of endosteal new bone which unites with the endosteal new bone of the host. New bone is formed by the activity of the endosteoblasts in all parts of the graft, centre and periphery."

Lewis (1914): "Cortical bone free from its periosteum, endosteum, and marrow will retain its vitality and proliferative power when subdivided into small fragments and replaced into the tissues. Contact with living bone is unnecessary for the growth of the transplant; larger pieces of bone may be transplanted and remain alive, not being merely grown into by the bone in which they come into contact." "Bone may unite after a fracture, or a space fill in after resection without the aid of any periosteal or bony bridge." "Contradictory results of careful observers can be explained by the variation in one factor, namely, the amount of blood supply which the transplanted bone obtains."

Bancroft (1914), in discussing the process of repair of bone following trauma, states that "one is impressed with the idea that the calcium salts have been laid down upon ordinary granulation tissue in the perivascular spaces; that is, in the area farthest away from the bloodvessels. This is early formation of new bone."

Mayer and Wehner (1914) state "that under favoring conditions many bone cells of the transplant can maintain their vitality until the transplant has become vascularized. The cells of the Haversian canals, particularly of the young bone, possess osteogenetic power provided their vitality is maintained. A greater part of the transplant necrosis, and that these necrotic areas are gradually replaced by new bone derived from the specific osteogenetic cells of the periosteum, endosteum, and Haversian canals. In bone transplants the bone cells showed no new formation of bone. A part of the transplanted bone dies, another part lives until the transplant is vascularized. The dead bone is partly dissolved by the young bone cells, which form new bone at the same time, which is gradually substituted for the old bone and penetrates into the old bone cavities."

Gallie (1914): "Death of the bone graft by the end of the first week. Revascularization of the graft by the second week. That in bone grafts as well as in living bone, bone absorption and bone building are the properties of living bone cells. By the end of the third week the graft is completely covered by new bone."

McWilliams (1914): "Living bone grafts have life inherent in themselves and are capable of permanent growth even when transplanted into soft parts."

Phemister (1914): "Osteogenesis in bone repair occurs from the inner layer of the periosteum, from the endosteum, and to a much less extent from the bone cells and fibrous content of the Haversian canals. The great mass of bone cells being away from the surface and surrounded by an extensive and difficulty permeable calcified matrix gradually undergo necrosis and absorption. A few (bone cells) about the periphery and lining the larger vascular spaces as well as the fibrous elements of the latter may survive and proliferate. A fracture through a transplant unites by callus formed from the surviving cells of the transplant in the vicinity of the fracture."

Macewen (1912): "The vegetative capacity of the bone cell is at least as great as that of the epithelial cell. Diaphyseal bone graft lives and actively proliferates in its new surroundings. That diaphyseal bone is produced by the proliferation of the osteoblasts derived from the preëxisting osseous tissue. As long as the bone cell remains embryonic, it exhibits the power of proliferation; when it reaches maturity it assumes the fixed tissue type and becomes stationary. This period is coincident with the calcareous deposition, and with it the cessation of active regeneration, though

its proliferating potentiality still remains. The regeneration of bone is proportionately in inverse ratio to the size of the graft. The vegetative capacity of the bone cell is as great as that of the graft. The vegetative capacity of the bone cell is as great as that of the epithelial cell, and if one grants not only the vitality of the transplanted epithelium, but also its power of extensive proliferation, then, judging by analogy, the bone cell ought to show equal capability of living and growing when transplanted."

That practically all the bone cells of the transplant necrose is supported by Barth, Bonome, Marchand, Saltykow, Axhausen, Frangenheim, Baschkirzew, and Petrow, while the theory that the graft retains its vitality and proliferates is supported by Macewen and McWilliams. Phemister is inclined toward the former view, but states that the bone cells about the periphery of the graft may survive and proliferate. No doubt the process involved is as complicated as the structure is complex, and no one theory will explain the changes in detail.

Method of Study. The studies of the regeneration of bone in this article are based upon the histopathological changes produced at varying periods of time after the operative procedures. The operative procedures were confined entirely to the practical application of the transplant, such as medullary transplantation, either cortex of the crest of the tibia or fibula complete, excluding macroscopic evidence of the periosteum; inlay transplantation, using an osteoplastid containing a full quota of elements, periosteum, endosteum, and compact bone, placed in apposition to its corresponding layers of the host. All experiments were performed on dogs, rabbits, or sheep, constantly employing the isoplastic or homoplastic methods. While these methods of experimentation are not entirely satisfactory, due to the dual process of repair going on simultaneously, *i. e.*, repair of fracture and regeneration of the transplant, nevertheless the exact duplication of the practical application of the problems and the complexity of the structure under consideration is so great that each individual element cannot be studied separately, the method outlined above is not without its favorable points. Many experimenters have endeavored to separate the various constituents of bone by removing periosteum and transplanting each singly to determine its bone-forming capacity. These have been only futile attempts, as it has been shown elsewhere that it is impossible to remove the periosseous layer of osteogenetic cells with the periosteum without at the same time removing a considerable portion of the cortex. Any attempt that has been made has been a recourse to false security and is unscientific.

Four Factors Involved in the Successful Transplantation of Bone. When an osseous transplant is transplanted into bone, either to fill in a loss of substance or to lend mechanical support

to the ends of a fractured bone, there are certain chemical, physical, and physiological demands placed upon the transplant itself, and also upon the adjacent tissues of the host, namely:

1. Temporary maintenance of nutrition not lower than the minimum compatible with the retention of the complete internal assimilation of the various elements of the transplant.

2. Permanent establishment of a sufficient pabulum for the transplant, by the revascularization of the Haversian system of the transplant from the necessary constituents both of the host and the transplant.

3. Complete osseous union between the transplant and the host.

4. Eventual metamorphosis of the transplant into an osseous entity complete in its contiguity with the adjacent tissues of the host.

Law of Functional Adaptation. Bone transplanted into bone, for specific and physiological reasons, subjected to varying stress and strain, will eventually be governed by the same laws as any other tissues under similar physiological demands. Normal tissues react both to their environment and functional requirements, as pointed out by Wilhelm Roux and known as the law of functional adaptation. This law may be stated as follows: The relation of the conformation, size, and architectural structure of any tissue or organ is dependent upon the functional demands placed upon that tissue; also, any variation in either of these demands will produce histological changes in the tissues sufficient to meet these variations. Transplanted tissues are not exempt from these conditions, and bone transplanted into a defect in bone, to supply a physiological demand and to perform specific functions, will undergo specific changes in its structure commensurate with these demands, *i. e.*, those bone cells retaining a sufficient reserve force to overcome the temporary enforced decrease in pabulum will eventually hypertrophy, subsequently take the place of necrotic bone, and finally functionate in their new locality. This hypertrophy of transplanted bone is well shown in those cases where a complete fibular graft is transplanted into the defect in the tibia. In a remarkably short time the fibula will increase in diameter by the circumferential deposition of new lamellæ. The hypertrophy may be either local or general, and is dependent upon the local application of increased strain upon certain portions of the graft, as in the case of muscle pull or stress applied over its entire structure. Certain functional demands upon the graft are necessary for its future welfare, for in those transplants where there is neither physiological nor mechanical function to perform, while the cells will retain their vitality, their proliferative activity will be materially decreased. Transplanted tissues upon which no functional demands are made will gradually diminish in size, as clearly demonstrated by Lewis and Davis in transplanted tendons, and also by Halsted, who demonstrated that

parathyroid tissue would undergo absorption unless a partial parathyropriva primarily existed. No doubt these conditions account for the absorption of the osteoplastid transplanted into certain muscles. Lack of functional demands causes atrophy and absorption.

Because of the tendency to use terms involved more or less loosely, an attempt will be made to limit their application to certain specific entities: Does the term bone cell refer only to the mature cell encased in its calcified matrix? If it is employed in such a sense, then we cannot refer to its vegetative capacity. The term should be applied only to the end stage of development of the osteoblast, encased in its calcified matrix, and in this sense it retains its inherent vitality; but as to its "vegetative potentiality," it is very doubtful. It will not be employed as a collective term, including the osteal fibroblast and its subsequent developmental stages. The osteoblast is a derivative of the undifferentiated osteal fibroblast, and represents a stage of differentiation between the fibroblast of the periosteum, endosteum, and Haversian system and the mature bone cell.

The Fate of the Bone Transplanted during Infection. The behavior of the transplant in the presence of an infection will be given special attention. The changes brought about in the transplant as a result of an infection will depend (1) primarily upon the virulence of the infecting microörganism, and (2) upon the different elements which constitute the osteoplastid, viz., the presence or absence of the periosteum will materially influence the extension of the infecting agent while the location of the infecting organism may account for non-union or even fracture of the transplant. Moreover, an infection of the marrow substance of a fibula transplant will add a serious complication, necessitating a second operation and detraction from satisfactory end results.

In the case of a fibula transplant there are three distinct sites of infection, *i. e.*, the marrow and either end of the transplant. A mild infection may be taken care of by the serum of the host if occurring at either end of the transplant. The process of repair at either end would be considerably delayed, depending upon the recognition of a suppurative osteomyelitis and the establishment of sufficient drainage. A properly fitting fibula transplant immediately restores the continuity of the bone, and in case of infection also seals up the active microörganism, which may demand drainage in the future. In the presence of an infection of more or less virulence the transplanted tissue, within its sphere of toxic influence, will undergo necrosis. Infection in a tibia (crest) transplant if suppurative will eventually establish a sinus sufficiently large to take care of the necessary drainage. At the line of fracture the process may become localized, and by necrosis and absorption of the transplant in this region may become so weakened as to fracture at this site.

Infection of the transplant with an established sinus does not effect the eventual formation of the external callus, but rather acts as a stimulus to osteogenesis, and an excessive callus is laid down with the immobilization of the fragments. However, an infected transplant will demand removal, since bone dissolution and absorption is very slow, taking months to remove a small transplant.

As the process of infection in other types of transplants, *i. e.*, transplants with the periosteum intact, quoting from Phemister, "these structures (periosteum and medullary substance) may survive and have a reëstablishment of circulation despite the mild infection. The surviving periosteum forms a new layer of bone about the cortex, which both in its excessive amount and in its coarse, spongy character resembles the involurum surrounding the involved shaft in osteomyelitis." "Absorptive changes in the dead cortex are very much accelerated. The surface is eroded, the Haversian canals are dilated, and since deposition of new bone does not keep pace with bone absorption the cortex is rendered somewhat porous in structure."

Glass-tube Experiment. The humerus of an adult rabbit was cut in two near the condyles and a compact isobone graft was transplanted into the medullary cavity of the distal end, allowing about 2 cm. to project out. Over this free portion of the osteoplastid was placed a glass tube which was sealed at one end and the other end was driven over the distal end of the humerus. The internal diameter of the tube about the transplant was about three times the diameter of the graft. This portion of the tube immediately filled with blood clot, completely surrounding the graft with nutrient plasma. Muscles and hide were sutured with silk. After six weeks the rabbit was bled and the transplant was examined. There was slight proliferation of the osseous tissue about the sawed end of the humerus and also necrosis and absorption about the circumference of humerus from the tight-fitting glass tube. The graft immediately adjacent to the end of the humerus had not increased in diameter, but the free end of the transplant had increased to at least twice its former diameter by circumferential deposition of new bone. While most of the mature bone cells had disappeared, there was evidence of active proliferation of the osteoblasts, especially about the circumference of the distal portion of the transplant.

If transplanted bone (non-infected) is undergoing a process of continuous absorption, as is claimed by some observers, why do we not find more frequently the endothelial leukocyte and the foreign body giant cell—the osteoclasts of Kölliker—for bone absorption cannot proceed by any other process? Osteoclasts in the majority of microscopic sections of transplanted bone must be searched for, and are not nearly as common as the literature would lead us to believe. While it must be admitted that even

isobone will undergo absorption in some animals, just as heterobone is absorbed in the majority of untreated animals, nevertheless, it is only the occasional animal in which the isobone transplant is absorbed, and far from the majority. Even heterobone has been known to remain in the human body for years (sheep to man, Drew) and perform its function.

In some cases the absorption of the isobone has been known to be dependent upon the treatment of the osteoplastid. The bed for the transplant must by all means be prepared first and the osteoplastid removed and transplanted immediately, and with

Transplant in glass tube, six weeks after transplantation.

very limited manipulation. Small grafts placed in bichloride of mercury (1 to 50,000) for three minutes were always absorbed, likewise grafts were absorbed when the hands were carelessly washed in bichloride (1 to 2000) and rinsed in sterile water. This procedure was at times accompanied by signs of necrosis about the prepared bed. Alcohol (1 to 20,000) for five minutes is extremely injurious to the graft, and its use was always associated with absorption. Freezing, while it has been successful with some tissues, has been unsuccessful in this series of experiments. Heat (110° F.) has been extremely injurious, and has been the source

of considerable trouble in the human transplantation of bone. It is not out of the ordinary to record a temperature of 160° F. taken from the saw immediately after going through three inches of cortex and exercising considerable care. If it is necessary to depend upon the bone cell in the periphery of the graft for its future maintenence, as there are sufficient indications at present to substantiate this view, then it is of paramount importance not to allow the saw to become heated. A few other antiseptic solutions, such as are found in the armamentarium of any well-equipped operating room—mercury cyanide, formaldehyde, etc.—were experimented with. The results were about equal to those cited above.

THE FATE OF THE MEDULLARY ISOBONE TRANSPLANT.[2] *Early Absorption of the Transplant.* Absorption of neither isobone nor heterobone is due to "changed serological relations," as has been claimed by certain observers, since as it has been clearly shown by Lambert and Hanes that transplants are capable of maintaining their vitality, *in vitro*, under artificial incubation, in heteroplasma of a limited variety of species, from which one readily concludes that absorption is not due to a lack of proper food material but rather to some inherent capacity of the cellular elements of the blood or surrounding tissue. Whatever inherent power produces such biochemical differences as to promote autolysis and absorption of the isoplastid, it is certain that the process differs from that which produces absorption of the heteroplastic, the former being dependent upon the bloodvessels and stroma (Bashford) while the latter is dependent upon an immunization process and the action of the macrocytes.

The absorption of the isoplastid, due to sensitization by foreign proteids (production of specific (?) ferments), is one factor which will occasionally account for the disappearance of the graft in a very short time, although in such a delicate process as the transplantation of living tissue, absorption may be brought about by many other factors.

More mature bone cells in the periphery of a graft will retain their vitality than in its central portion. Therefore, more bone cells will retain their vitality per unit of mass of transplant in a complete fibular transplant with two surfaces of the compact bone in contact with the plasma of the host than could be expected in a tibial (crest) transplant with only its external surface in contact with the surrounding plasma. Correspondingly more of the calcium saturated matrix will remain intact, since it is directly under the influence of the mature encased bone cells. The fibulaplastid will require less absorption and replacement than a tibiaplastid,

[2] These remarks apply only to a periosteal-free compact bone transplant placed in the diaphysis and do not refer to bone transplanted in cancellous tissue in proximity of the epiphysis.

and therefore the surrounding tissue reaction will cease earlier, viz., shorter convalescence.

Early Changes Immediately Adjacent to the Transplant. The space between the bone of the host and the osteoplastid where it is not in direct apposition will immediately become filled with coagulated blood and lymph. The clot in time will undergo organization, with the formation of osteoid tissue through which new capillaries will push themselves to the osteoplastid and form a network of fine anastomosing capillaries around its surface. From this vascular network small capillaries are seen to enter the empty Haversian canals.

At either end of the graft a blood clot will be formed, the size of which will depend upon the traumatism to the marrow substance. If the marrow substance has been injured by forcing the transplant against it, producing undue pressure, the changes at the end of the bone are delayed until the proper equalization of pressure is produced by necrosis and absorption. If the marrow has been removed for a sufficient distance, so that the osteoplastid does not produce pressure atrophy and necrosis of the marrow, then both ends of the transplant will be sealed off from the remaining marrow cavity by a blood clot. This occurs within the first twenty-four hours. The endosteum, which has been previously removed from the medullary cavity by curetting, proliferates, covering over denuded bone as far as the blood clot, and later will gradually extend across the concave surface of the clot, sealing off the proximal and distal medullary cavities from the graft by a limiting layer of endosteal cells.

The blood clot at either end of the graft extends farther up on the side of the medullary cavity than it does in the centre, forming a concave surface on the clot.

The blood clot gradually undergoes transformation into osteoid tissue, and in the case of the fibula transplant the osteoid material forms a plug extending into the medullary cavity of the fibula. The transformation of the clot into osteoid material takes place much more quickly than at the sides of the graft, *i. e.*, between it and the host. The calcification of the clot at the ends of the graft progresses quite rapidly, so at the end of thirty days both ends of the graft are solid in the marrow cavity.

The space between the ends of the fractured fragments become filled with clot which finally organizes, but for some unknown reason does not undergo calcification and ossification until many months later. (Approximately seven to nine months in the tibia of a dog, and if conditions are not favorable, this time is materially increased.) This delayed process of calcification is probably due to atrophy of the ends of the fractured fragments extending back from the ends to a varying distance. Not until regeneration has been completed in these atrophied ends does the cicatrix between the fragments undergo calcification and ossification.

This same process of delayed calcification takes place within the medullary cavity, and is especially marked when the transplant is not rounded to fit the medullary cavity. In this the edges of the graft under pressure undergoes necrosis and absorption by the osteoclasts until the pressure is equalized and compatible with the vitality of the surrounding living tissue. While the primary purpose of the medullary transplant is to immobilize the fragments, nevertheless any undue pressure between the transplant and the compact bone of the host will produce a delay in osseous union.

These processes of necrosis and absorption are retrogressive, and are not compatible with regenerative and reparative processes. Not until these retrogressive processes have completely subsided is it possible for any process of a reparative nature to take place. This simply means a delay in a process which is of primary importance, being secondary to immobilization and the proper coaptation of the fragments. Moreover the process of absorption is dependent upon the physical condition of the patient, and is commensurable with the variability of any such process in the human body. The end products of pressure necrosis and degeneration are conducive to excessive callous formation, and consequently detrimental to the complete restoration of function when the fracture is in proximity to a joint, causing limitation of motion.

Any tissue, such as muscle, fat, marrow (?), periosteum, endosteum, etc., which may find lodgement between the compact bone of the host and the transplant will produce a cicatrix which will not become calcified, producing merely a fibrous tissue union.

Finally the conformation of the new osseous development is dependent upon the balanced action of the formative osteoblasts and other cells, osteoclasts which remove any excess of spicules of bony development and mould the bone.

Some of the Haversian canals of the graft become filled with coagulated blood, which will cause necrosis and absorption of the osseous tissue of the area which the canal had supplied. These portions of the Haversian canals do not undergo revascularization, but are eventually replaced by the method of "creeping replacement."

Deposition of calcium in osteoid material at the ends of the transplant must not be mistaken on the interpretation of roentgenograms for absorption of the graft, since serial roentgenograms at weekly intervals demonstrate this area of lessened intensity to be progressive and not retrogressive, as must necessarily be the case in peripheral absorption. Invariably at the end of six months the medullary graft has increased in length and the spindle-shaped ends are due to progressive deposition of calcium in the osteoid material, which is deposited soon after the insertion of the osteoplastid.

Death of the Bone Cells. During the normal metabolic activity of osseous tissue the matured bone cell is constantly being

replaced by osteoblasts which have reached the stage of complete maturation. Whether the lacunar space occupied by the wornout bone cell is to be occupied by the new bone cell is not known, although after taking into consideration the complicated structure of the bone cell with its ramifying fibrils extending through the canaliculi it does not seem feasible that such a process of replacement were possible. All the stages of maturation are present at one time during the normal economy of osseous tissue metabolism from the fibroblast to the fully differentiated bone cell. If this is the case in normal bone development we should at least be prepared to accept the same conditions for transplanted bone. In the osteoplastid we find bone cells in all stages of destruction, which continue at a greater rate than in normal osseous tissue. From the second to the tenth day there appears no limit to their destruction. However in each cross-section many living bone cells are always found in the periphery of the graft, while in the central portion the majority will be found shrunken and dead. Many lacunæ are completely devoid of any cellular life, and the staining reaction of the calcified material in its neighborhood is the best guide for the interpretation of the death of the bone cell. Empty lacunæ do not necessarily mean dead bone cells, especially not with our present histological technic. Furthermore it must be remembered that a few bone cells in the host after curetting the endosteum will die, as already shown by Cotton and Loder. Occasionally after a bone cell has taken up its task of producing new bone in the transplant, as shown by the deposition of a few lamellæ of bone, the cell will be found shrunken and the staining reaction deficient. Evidently the bone cell did not have the necessary reserve force to hold out under such a difficult environment. The process of calcium deposition will immediately be assumed by another bone cell. The metabolic interchange in a transplant must necessarily be many times greater than normal to keep up with the increased tissue destruction and absorption.

Reëstablishment of a Permanent Circulation. In normal bone the Haversian canals contain several types of tissues, *i. e.*, the small artery, a large vein, a very narrow lymph channel, and cellular tissue. In the transplant all of these structures are seldom seen. Lymph vessels and veins have not been observed at any age of the transplant. The fine capillary network surrounding the graft, as described above, send fine capillaries into the substance of the transplant wherever it is possible to gain an entrance. No preference is given to the Haversian canals. Occasionally a small capillary has entered the graft only a few microns to the side of the Haversian canal, and shows no indication of preference for the canal. In the fibula transplant the capillaries pass through the compact bone and ramify with the capillaries of the marrow substance. As a rule, most of the Haversian canals show new-

formed capillaries, but some are filled up with a coagulated, structureless substance with no indications of bloodvessels.

In constant association with the new-formed capillaries are seen numerous large cells which vary in morphology, and are no doubt maturing bone cells. They are situated on the outside of the vessel wall; sometimes, especially in large Haversian canals, they are in no relation to the bloodvessels, with the exception that they are invariably present. Occasionally these cells have been seen to occupy recesses in the calcified matrix at the side of a small capillary.

The reëstablishment of the permanent circulation is one of the most important stages in the life of the transplant, since not even a beginning of capillary proliferation has been observed in those heteroplastic transplants which sometimes are so readily absorbed. This same process has been seen in heteroplastic transplants taken from the most varied species (pigeon to rat), although a large percentage shows no evidence of capillary proliferation at all.

In the fibula transplant the capillary circulation throughout its marrow substance is readily established, aiding in an early supply of pabulum to the compact bone.

Methods of New Bone Deposition. In any transplanted bone considerable new bone must be laid down to insure the continuity of the graft. In the normal living bone this new bone is almost entirely supplied by lacunar deposition. In transplanted bone, while Axhausen maintains that lacunar absorption and subsequent bone apposition are sufficient to explain the replacement of all new bone, nevertheless, replacement of osseous tissue by direct contiguity—so-called "creeping replacement" (Schleichender Ersatz)—is frequently observed. Bone absorption and bone building are properties of developing and mature bone cells. Bone is absorbed with the liberation of carbonic acid (Hofmeister) setting free the earthy salts for the synthesis of the new bone by the mature bone cells.

The necrotic bone becomes absorbed under the influence of the mature bone cells and new bone is deposited, layer after layer, by these same cells. This process is constantly being observed in all sections of transplanted bone. Occasionally the necrotic bone is replaced by tissue laid down in its immediate vicinity by young bone cells which produce changes in this dead bone by the fibrils which penetrate its substance, and in this way gradually exert sufficient influence over it to produce absorption and deposition of new bone.

Metamorphosis of the Entire Osteoplastid into a Complete Osseous Entity. With the complete reëstablishment of the circulation and deposition of new bone for the necrotic calcium saturated matrix the osteoplastid becomes, after many months, an osseous entity directly continuous with the adjacent osseous

tissue of the host. All osseous transplants will not progress to this same degree, since some transplants stimulate osteogenesis to a greater extent than others, producing a large callus sufficient to supply the necessary mechanical demands placed upon it. In such a case the osteoplastic would no longer be required, and its metamorphosis may be discontinued at any stage of the transformation. The time necessary for the complete metamorphosis of the osteoplastid depends upon the size of the graft, condition, and age of the host, and will vary from one to two years.

Final Absorption of the Transplant. The transplant is not a permanent entity, since a gradual decrease in the functional demands is associated eventually with the complete absorption of the graft. This is shown very early in transplants placed in the medullary cavity of the humerus[3] for the repair of recent fractures. In this location in a healthy individual all mechanical demands are removed early with a corresponding early absorption of the osteoplastid. In one case[4] after an excellent result the transplant is undergoing absorption as early as the fourteenth month after operation. Complete absorption will take place in from two to five years, depending upon the size of the graft, age of the patient, and the place of its insertion.

CONCLUSIONS. 1. Osteogenesis is not a specific attribute of any tissue or layer of cells, but is limited entirely to the osteoblasts which are scattered throughout the entire structure of the osteoplastid and the host.

2. Mature bone cells are end products, and while they may undergo mitosis under artificial conditions, this proccess is unknown in the human economy.

3. Many mature bone cells of a transplant remain alive, especially near the periphery of the transplant, and control its surrounding calcified matrix.

4. Absorption of isobone is influenced in many cases by the treatment received by the transplant.

5. Protoplasmic poisons should not be employed during bone-grafting procedures.

6. Regeneration of bone for the most part is an indirect process through the differentiation of the osteoblast to a mature bone cell.

7. A transplant is subject to the varying demands of its environment; functional demands producing an increase in bone deposition; lack of functional demands causes atrophy and absorption.

8. Bony contact is not essential to regeneration of bone, but for practical purposes, doubly insures the result desired.

9. In the transplantation of any bone, the most that can be hoped for is the continued development of the implanted osteoblasts,

[3] Absorption is not the rule when an entire humerus is replaced by a complete fibula transplant, as in case of sarcoma of the humerus.

[4] Case to be reported by Dr. Charles Davison.

together with such stimulus as may be obtained from the osteoblasts of the host and the retention of vitality in some of the transplanted bone cells with their corresponding intercellular calcium matrix.

10. The transplant in the presence of an infection may or may not survive, and is dependent upon the type of the infecting agent.

11. The medullary transplant is not a permanent entity, but is absorbed as soon as all functional demands are removed.

BIBLIOGRAPHY.

Albee. An Experimental Study of Bone Growth, etc., Jour. Am. Med. Assn. lx, 1044.

Allison. Direct Implantation of Bone Graft, Surg., Gynec. and Obst., 1910, x, 303.

Axhausen. Histologisch. Untersuch. ber Knochentranspl., Deut. Zeit. f. Chir., 1907, Bd. xci.

Axhausen. Die Histolog. und klin. Gesetze der Frei. Osteoplast, Archiv f. klin. Chir., 1909, lxxxviii, 23.

Bancroft. Process of Bone Repair following Trauma, Am. Jour. Med. Sc., June, 1914, p. 809.

Barth. Ueber histologisch. Befunde nach Kochenimplant, Archiv f. klin. Chir., 1893, Bd. xi.

Barth. Histologisch. Untersuch. ber Knochen, Ziegler's Beitr., xvii.

Bond. Tranplantation of Fibula: Process of Growth, British Jour. Surg., 1914, i, 610.

Bonomme. Zur histogen. der Knochenregeneration, Virchows Archiv, 100, 293.

Colvin. A Brief Summary of Bone Regeneration, Surg., Gynec. and Obst., 1907, v, 666.

Cotton and Loder. The Fate of the Bone Graft, Surg., Gynec. and Obst., 1913, xvi, 701.

Frangenheim. Dauerfolge der osteoplastik, etc., Archiv f. klin. Chir., 1910, xciii, 191.

Gallie. The History of the Bone Graft, Am. Jour. Orth. Surg., 1914, xii, 201.

Janeway. Autoplastic Transplantation of Bone, Ann. Surg., 1910, lii, 217.

Korschelt. Regeneration and Transplantation, Jena, 1907.

Lewis. Preliminary Report of Experimental Work on Bone, Surg., Gynec. and Obst., xviii, 572.

Lexer. Free Transplantation, Ann. Surg., lx, 137.

Macewen. The Growth of Bone. Glasgow, 1912.

McWilliams. Is Contact with Living Bone Necessary for the Life of the Graft, etc., Jour. Am. Med. Assn., January 31, 1914.

Nicholls. Osteomyelitis, Jour. Am. Med. Assn., 1904, xlii, 439.

Marchand. Die Wundheilung, Leipzig, 1901.

Nemiloff. Experimental Study of Bone Transplantation, Chir. Archiv, Veliaminova., 1914, xxx.

Ollier. Traité de la regeneration, t. 1–2.

Orth. Ein Beiträg zur Kentniss des Knochencallus, Berlin. klin. Wchnschr., 1906, xliii, 430.

Petrow. Quelle der Regeneration bei Knochen berpflanz, Archiv f. klin. Chir., cv, No. 4, 769.

Phemister. Fate of Transplanted Bone and Regenerative Power of its Various Constituents, Surg., Gynec. and Obst., xix, 303.

Schöne. Die heteroplastische und homoplastische Transplant, Berlin, 1912,

Streissler. Beiträg. z. klin. Chir., 1910, vii.

Thomas. Bone Transplant, Surg., Gynec. and Obst., xviii, 580.6

Tomita. Experimental Research on the Transplantation of Bone, Virchows Archiv, 1908, cxci, 170.

Wetherhill. The Growth, Death, and Regeneration of Bone, Jour. Am. Med. Assn., 1913, lx, 983.

Cornil and Coudray. Du cal. au point dé vue exp. et histol., Jour. de l'anat. et physiol., 1904, xl, 113.

REVIEWS

PULMONARY TUBERCULOSIS. By MAURICE FISHBERG, M.D., Clinical Professor of Tuberculosis, New York University and Bellevue Hospital Medical College; Attending Physician, Montefiore Home and Hospital for Chronic Diseases, New York. Pp. 639; 91 engravings and 18 plates. Philadelphia and New York: Lea & Febiger, 1916.

IN the author's words, "It is the purpose of this book to supply the general practitioner with information concerning the etiology, diagnosis, prognosis, and treatment of pulmonary tuberculosis, its clinical forms and common complications." He has had an experience of eighteen years with tuberculosis problems in New York City to fit him for the task. Great pains have been taken to present the many varied subjects in a broad way, and at the same time to keep them within proper limits. The constant evidences of the author's own experiences, and his frequently expressed personal opinions, stamp the book with distinct individuality. Good sense and judgment are frequently displayed, for example, in advising physicians to tell their patients when they are suffering from tuberculosis, and in warning the general practitioner against using tuberculin in treatment. The author's wide reading, and the many references furnished, add greatly to the value of the volume. Among the good features of the work are the emphasis laid on the great importance of the home as a factor in the problem of tuberculosis, especially in regard to treatment, the importance attached to the constitutional symptoms in deciding whether a person is ill from tuberculosis, the importance of tuberculosis in the aged, and the importance of economic conditions as affecting the diminution of tuberculosis. Under physical diagnosis it is a pleasure to see the amount of attention given to inspection. The treatment of pulmonary tuberculosis is based on personal experience and considerable reading, and many of the requirements for handling this important subject have been fulfilled. The illustrations and index are a great help to the volume.

On some subjects more could have been said with advantage, for example, about differential diagnosis, about anesthesia in operations on tubercular patients, and about the treatment of tuberculosis complicated with pregnancy. The subject of vocal fremitus receives very little attention. It would have been profitable to

discuss the value to medical men, both students and physicians, of clinical instruction in tuberculosis.

The author is profoundly impressed by the evidence favoring the theory that the adult human being is in very slight danger from exposure to tubercle bacilli outside himself, because of a supposed immunity developed in childhood, and his belief in this theory has greatly colored his practical suggestions in regard to prophylaxis. It is to be feared that some who read this book may fail to sufficiently realize the great importance of the prevention of tuberculosis, about which too much care cannot be observed along a good many different lines, at least so long as a great number of problems regarding the dissemination of this disease remain only imperfectly solved.

There are a variety of opinions and statements in the book that are liable to adverse criticism. Thus it is stated, in speaking of auscultation of normal persons, that "there are many individuals in whom bronchial breathing is heard all over the upper parts of the thorax" (p. 282). In another place it is asserted that "rales are only produced when the caseous material softens and breaks through the wall of a bronchus" (p. 283). Profuse hemorrhages are said to be seen only in advanced consumptives (p. 199). According to the author, active phthisis is extremely rare in cases of heart disease (p. 196). The administration of the iodides is given as one of the methods for obtaining expectoration in early cases (p. 159). In some respects the directions given about exercise are too liberal (p. 476). I do not consider nasal breathing on the part of the patient during auscultation of the chest, as recommended by the author, to be as generally available as oral breathing. The propriety of submitting another classification of cases of pulmonary tuberculosis is open to question.

While unable to agree with the author on all points, the reviewer has derived much pleasure and profit from a perusal of these pages. The book is informing and is calculated to stimulate one's interest in many of the puzzling problems associated with pulmonary tuberculosis. C. M. M.

ELEMENTARY BACTERIOLOGY AND PROTOZOÖLOGY. FOR THE USE OF NURSES. By HERBERT FOX, M.D., Director of the William Pepper Laboratory of Clinical Medicine in the University of Pennsylvania. Second edition, revised and enlarged. Pp. 251; 68 engravings and 5 colored plates. Philadelphia and New York: Lea & Febiger, 1916.

THE scope of the book is indicated in its table of contents, which follows: Chapter I, introduction, history, place of microörganisms in nature; II, morphology, reproduction, chemical and physical

properties; III, general biology, including the chemical changes wrought by bacteria; IV, methods of study, sterilization by heat; V, destruction of bacteria by chemicals and their practical use; VI, relation to disease, immunity; VII, preparations for and procuring of specimens for bacteriological examination; VIII, the acute chiefly localized infections of pus nature, the pyogenic cocci; IX, the acute self-limited infections; X, the more chronic infectious diseases; XI, various pathogenic bacteria not associated with a specific clinical disease; XII, yeasts and moulds; XIII, bacteria in air, soil, water, and milk; XIV, diseases due to protozoa; XV, diseases of unknown etiology; glossary.

The reviewer can criticise but little adversely. On the other hand there are several features that stand out most prominently and favorably because they are unusual in a text-book for nurses: First and foremost the numerous and good illustrations. Second, descriptions of apparatus which the well-trained nurse may bring to the physician by naming (instead of description), as well as minor technical procedures. Again, the completeness of the book makes it perhaps a possible one for medical students, and certainly for that daily increasing body of laymen and women who occupy permanent and full-time positions in hospitals and other laboratories in technical capacities. F. D. W.

Diseases of the Stomach and Upper Alimentary Tract. By Anthony Bassler, M.D., Professor of Clinical Medicine, New York Polyclinic Medical School. Third edition. Philadelphia: F. A. Davis Company, 1916.

The third edition of Dr. Bassler's book is from the press and the work is too well known to merit any extended summary. The edition is amplified by a more extensive contribution to Roentgen-ray diagnosis and the inclusion of a number of half-tone plates which considerably enhance the value of the book. Diseases of the mouth, esophagus, and stomach are discussed in different chapters, and the whole is compiled in a thoroughly readable volume which has already had the approbation of the medical public. The chapter on laboratory diagnosis is satisfactory, and the chapter on feces is one of the best which has appeared in a work of this nature.

After discussing the anatomy, physiology, and chemistry of the stomach, chapters are devoted to the various laboratory procedures, clinical examination, therapeutics, medicinal treatment, physical methods of treatment, surgical indications, and finally the various organic and functional conditions of the upper alimentary tract.

The work is simply a revision of the former volumes and presents the subject in much the same way. It is, however, more decidedly

clinical than scientific and from the stand-point of the practising physician more readily assimilated. From a critical stand-point, however, fault can be found with the work in that it is written too much from the stand-point of the gastro-enterologist *per se*, rather than from the logical view-point of gastrology as merely one of the highly specialized departments of internal medicine. Not enough insistence is placed upon the fact that many abdominal conditions are other than stomach and bowel, and in the opinion of the reviewer no work on diseases of the stomach is complete unless it presents in a cursory way gall-bladder, pancreatic, and ductless gland syndromes whose chief symptoms frequently masquerade in the region of the epigastrium. Furthermore, the definite tendency of internal medicine to become essentially analytical has not been sufficiently emphasized. We are slowly getting away from dyspepsia and chronic gastritis and reaching causes and effects.

Autonomic imbalance, and the whole question of sympathicotonia and vagotonia is merely skimmed over; aërophagia is not discussed in the light of recent knowledge; the newer secretory and motor investigations have been entirely overlooked. Such statements occur as "the gastric juice is not secreted in its normal state excepting during the process of digestion in the stomach," is at variance with recent discoveries. Frequently statements are confusing, such as, for instance, p. 36, "The first morsels of a meal take a general course anywhere in the organ, until a certain quantity of food is contained in the viscus, although Roentgen-ray observations with a fluid bismuth mixture show that foods drop directly downward from the cardia to a vertical point at the greater curvature and then flatten out there before they coat the inside of the organ," a statement which any radiographer will contradict, especially since long ago it was pointed out by Leven, Barret, Holzknecht and others, that even as little as 30 c.c. of liquid was sufficient to fill the so-called normal empty stomach, owing to its peristole function, and any real tendency toward flattening out is suggestive of atony.

We would suggest that Sippey's method be considered in the treatment of ulcer, that reference be made to the Haudek "nischen" symptom in penetrating ulcer. The tests for neoplasm, such as the protein concentration, formol index, antitryptic serum reactions, while none of them specific, might be included, as anything which will throw light on the possibility of this lesion should be emphasized. There is, furthermore, in this work, no consideration of gastric volvulus, subdiaphragmatic hernia, and the by no means rare achlorhydria hemorrhagica gastrica of Pilcher, which should be discussed in a work of this nature.

Apart from these points, which should be included and the references which are somewhat out of date, the book is to be recommended as a safe and sane exposition of diseases of the upper gastro-intestinal tract. Dr. Bassler is to be commended for the

stand he takes on gastroplication and gastropexy as being unwarrantable surgical procedures, as well as the recommendation that the woman who is predisposed to ptosis should wear a satisfactory binder after labor, a point which many physicians entirely overlook. The book is full of much practical information, which cannot fail to be of value to the practising physician. M. E. R.

TASCHENBUCH DES FELDÄRZTES. II Teil. Herausgegeben von Generalärzt Professor Dr. Ad. DIEUDONNÉ, Geheimrat Professor Dr. M. v. GRUBER, Professor Dr. H. GUDDEN, Oberstabsärzt z. D. Dr. W. HASSLAUER, Privat-Dozent Dr. W. HEUCK, Stabsärzt Professor Dr. FR. SALZER, Oberstabsärzt Professor Dr. Gg. SITTMANN, Professor Dr. W. SPIELMEYER, Professor Dr. W. WEICHARDT. S. 238, mit einer Tabelle und 12 Abbildungen. München: J. F. Lehmann's Verlag.

UNLIKE the manual of war surgery by Delorme, which was recently reviewed in these columns, this little work was designed to serve as a *vade mecum* for the common diseases that are inseparable from camp-life. The subjects dealt with are exactly those which are encountered in the daily routine of a busy medical out-patient department. Thus, brief working abstracts are given, among the contagious diseases, of typhoid fever, grip, gonorrhea, lues, tetanus, etc.; among the thoracic diseases, of acute cardiac failure, functional heart disturbances, bronchitis, and tuberculosis; among nervous diseases, sunstroke and thermic fever, neuralgias, herpes zoster, neuritis, hematoma of the dura mater; among psychic disturbances, dementia precox, epilepsy, alcoholism, contusion psychoses and neuroses. The common affections of the eyes, ears, nose and skin are also covered in brief.

The book is eminently practical throughout, presents modern methods, and is useful in refreshing the memory on medical minutiæ.

P. G. S., JR.

DIE OPERATIVE BEHANDLUNG DER LUNGENTUBERKULOSE. Von Prof. Dr. F. JESSEN, Davos. Würzburger Abhandlungen aus dem Gesamtgebiert der praktischen Medizin. S. 56, mit 8 Abbildungen im Text. Würzburg: Verlag von Curt Kabitzsch.

THIS brochure serves a good purpose by pointing out to the practitioner the possibilities of the surgical treatment of pulmonary tuberculosis, when the cases are properly selected. There are considered in order extirpation of the tubercuous lung; the open-

ing of cavities; artificial pneumothorax; extrapleural thoracoplasty; plugging of cavities and pleurolysis; phrenicotomy and stretching of sympathetic cord; ligation of pulmonary artery; and operations upon the superior aperture of the thorax. The greater part of the monograph is devoted to the consideration of artificial pneumothorax, and in this subject are included very instructive diagrams.

From the nature of the malady it holds that the results of the present-day operative treatment of pulmonary tuberculosis are not so favorable as surgery upon healthy patients has to offer; but the operative treatment enables one to help—even cure—many patients who without it would have succumbed. When the indications for operation are urgent, the risk in proportion to the amount of benefit that may be derived is very slight. The surgery of pulmonary tuberculosis needs further development, but has already become indispensable: it should be combined with general hygienic and dietetic tuberculous measures. As Sauerbruch once observed, advanced pulmonary tuberculosis is more of a mechanic than a constitutional bacterial problem. The hope of the future is to combine operative procedures with climatic and chemic treatment.

The brochure throughout gives a good outline of the present state of the operative treatment of pulmonary tuberculosis.

P. G. S., Jr.

Cancer of the Stomach. By Frank Smithies, M.D., Gastro-enterologist to Augustana Hospital, Chicago; formerly Gastro-enterologist to the Mayo Clinic, Rochester, Minn. With a chapter on the Surgical Treatment of Gastric Cancer. By Albert J. Ochsner, M.D., LL.D., F.R.C.S., Professor of Clinical Surgery in the School of Medicine of the University of Illinois. Pp. 522; 106 illustrations; 41 tables. Philadelphia: W. B. Saunders Company, 1916.

This book is undoubtedly the best contribution to the subject of gastric cancer that has as yet been published. While the author in his preface rightly admits that it is by no means the "last word" upon the subject, nevertheless it is the latest one.

The material for this book is based upon the study and analysis of 921 cases of cancer of the stomach largely from the Mayo Clinic at Rochester, Minn., and most important of all is the fact that each case studied has been operatively and pathologically proved to be cancer. The author is therefore dealing with facts and not fancies —facts that have been secured by painstaking perseverance and recorded in detail and the interpretation of these facts has been made by a clinician of wide experience and one whose interests are largely centred in the problems of the gastro-intestinal tract.

Furthermore, there has been a most happy coöperation between the clinician, the clinical and radiographic laboratories and the surgeon, a combination that is indispensable to the diagnosis of early cancer. Here may be mentioned the only criticism that is offered and that is the failure of the insertion of tables giving data as to surgical end-results. Here lies the proof of the pudding.

The book is divided into eleven chapters by Smithies, which completely cover the subject from the standpoint of etiology; morbid anatomy; symptomatology; physical examination; diagnostic laboratory tests; Roentgen examinations; differential diagnosis; non-surgical treatment and an especially important chapter on the significance of gastric ulcer with respect to gastric cancer. There is in addition one chapter ably handled by Ochsner on the surgical treatment of gastric cancer. All chapters are good. The morbid anatomy and diagnostic laboratory investigations are particularly well handled. In the chapter under symptomatology the author has made a notable contribution in dividing his cases into six groups with a differentiation of the types of case histories commonly met with. This is important and timely because the commonly accepted type is the classic text-book picture which applies to late rather than early cancer.

The book is printed on good paper, in large easily-read type, and the tables and illustrations are all good and have been selected and prepared with great care. One point to emphasize is the general readability of this monograph, and the author is to be congratulated upon his literary style.

This book should be in the hands of every practitioner who is interested in this subject, and could well be made a monographic text-book in our medical schools. B. B. V. L.

A Text-book upon the Pathogenic Bacteria and Protozoa. For Students of Medicine and Physicians. By Joseph McFarland, M.D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College, Philadelphia. Eighth edition, thoroughly revised. Pp. 807; 323 illustrations, a number of them in colors. Philadelphia and London: W. B. Saunders Company.

The eighth edition of McFarland's deservedly popular book will be received with pleasure and profit by those accustomed to use the previous editions. The new edition appears in larger page form than the previous edition, indicating that the type has been reset, but sufficient material has been added to keep about the original number of pages. Many beautiful illustrations have been added.

Dr. McFarland has adhered to the division of his book into two parts, the first on general bacteriology and technic; the second devoted to special diseases. The chapter on bacterio-vaccines is not all that could be desired. There is not enough said of the practical application of vaccine therapy, and the only method given for counting a vaccine is the inaccurate method of Wright; direct counting in a blood counting chamber, or preferably in a special chamber such as the Helber is not even mentioned. The technic of the Wassermann reaction is not given with the clarity of style one finds in the rest of the book. It seems to the reviewer that a more detailed description of the various accepted technics would be an improvement. The space devoted to antiseptics and disinfectants and their use is well allotted; too often do we find these subjects and their practical application but skimmed over.

The second part of the book, devoted to special diseases and their germs, is presented as before in rather curious order. Toxic and endotoxic diseases, acute infections and protracted diseases, protozoal and bacterial—all are given together, with apparently no systematic arrangement. It would appear to be better to present the diseases according to some classification. It might not be amiss to devote a separate section to protozoal diseases.

The author is to be congratulated on the addition of some of the diseases due to filterable viruses in the new edition. As bacteriological and immunological methods are used in the study of these diseases it might be well to include all those conditions now attributed to filterable virus. H. F.

Diseases of the Throat, Nose and Ear. By William H. Kelson, M.D., B.S., F.R.C.S. (Eng.), Surgeon of the London Throat Hospital, Golden Square; Hon. Surgeon (Nose, Throat and Ear Department), City Dispensary; Lecturer on Diseases of the Ear. Pp. 252; 89 illustrations. London: Oxford Med. Press.

This work is a small text-book written for the general practitioner and the senior student. For this reason the more common and trivial procedures, such as the removal of cerumen, are given in considerable detail, while the more important undertakings, which are generally relegated to the specialist, are scarcely more than mentioned if not entirely omitted. We, however, see no reason why the author has failed to make any mention of such an important procedure as direct laryngoscopy and bronchoscopy. There is a lack of systematic arrangement of various subjects, and the style, to say the least, is exceedingly quaint. For instance, in speaking of pemphigus of the throat (p. 21) the author says "Arsenic

has a great reputation in this disease but most of the patients die." On the whole the book is a rather trite accumulation of throat, nose and ear lore giving many of the well-established facts their proper importance, and yet, it is sufficiently full of mistakes, especially concerning pathology and therapeutics to make it a rather unsafe guide for either the student or medical practitioner. The illustrations while fairly numerous are not especially illuminating, and the majority are crude and uninteresting. G. B. W.

STUDENT'S TEXT-BOOK OF HYGIENE. By W. JAMES WILSON, M.D., D.Sc., D.P.H., Bacteriologist to the Counties of Down and Antrim; Lecturer in Hygiene and Public Health, Queen's University, Belfast. Pp. 270; 26 illustrations. New York: Rebman Company.

HYGIENE in a strict sense deals with the principles of the science of keeping well, while public health, preventive medicine, and sanitary science have to do with the application of those principles. It is in this strict sense of the word that Wilson takes up the subject of hygiene in this book. The details of laboratory methods, the procedures of public health administration, and the technic of prophylactic measures are wisely omitted. The application of the principles discussed is only indicated in sufficient degree to enable the student, for whom the book is primarily written, "to appreciate the meaning and value of the results of analyses, and to understand the responsibilities resting upon the medical officer of health, the general medical practitioner, and the private individual, with regard to the preservation of health and the prevention of disease."

One is surprised to note the author's statement that "the routine inoculation of contacts with prophylactic doses of diphtheria antitoxin is not a measure which recommends itself to many physicians at the present time." Also, "In the British Isles open fires find favor on account of their cheerful appearance, while in America stoves are almost invariably used." Furthermore, one would not expect typhoid fever to be given in the list of diseases for which isolation hospitals should be furnished. T. G. M.

PHYSIOLOGICAL CHEMISTRY. A TEXT-BOOK AND MANUAL FOR STUDENTS. By ALBERT P. MATHEWS, Ph.D. Pp. 1041; 78 text figures. New York: William Wood & Co.

MATHEWS has given us in this work one of the best books of its kind in physiological chemistry which has appeared in the English

language in recent years. The author states in the introduction, "Some parts of this subject have been treated far more fully than others, and, possibly, more fully than their importance deserves." This might be considered a fault by some, but, as one's personal preferences guide him in his opinion, this could hardly be looked as upon a point for criticism. The book is divided into three parts: Part I deals with general properties of living matter: the usual separate chapters on carbohydrate, fat, protein, and a very interesting chapter on the physical chemistry of protoplasm. Part II deals with body heat, food, digestion, absorption, excretion, metabolism as a whole, and the various body tissues. Part III consists of practical work and methods. At the end of the important chapters there is found an excellent summary of the subject matter and also references to the literature. The subject matter is brought up to date and is presented in a lucid, fascinating, readable manner. The book is certainly to be recommended to students and others who are interested in biological chemistry. In view of the ever-increasing adaptability of biochemical methods in diagnosis the chapter on practical methods should certainly increase the value of this book to physicians. L. J.

LEJAR'S URGENT SURGERY. By FELIX LEJAR, Professor agrégé à la Faculté de Médecine de Paris; Chirurgien de l'Hôpital Saint Autaine; Membre de la Société de Chirurgie. Pp. 588; 1106 illustrations. Seventh edition, Vol. II. New York: Wm. Wood & Co.

THIS volume treats of the urgent surgery of the genito-urinary system, the rectum and anus, the hernias and the extremities. It is translated from the French by W. S. Dickie, M.D., and Ernest Ward, M.D.

The subject matter contained therein is all that could be desired. It treats of those phases of the conditions which are incompletely described and discussed in other works on surgery. No attempt is made to give a complete description of any one condition as regards pathology, etiology, etc. The reader is introduced to the urgent condition and then told how to handle it. Throughout the text there are numerous footnote histories of cases illustrating the condition under discussion.

After arriving at the diagnosis the author describes in minute detail the subsequent treatment, discussing the one or more possible ways of overcoming difficulties that may arise.

The illustrations and plates, aptly chosen and well executed, enhance the value of the work.

The style is exact, easy and pleasing, presenting facts, theories and opinions in an interesting and novel manner.

The book is well edited and the paper and printing are of the best.

When one takes up this work he is at once impressed by the author's vast and comprehensive grasp of his subjects, and by his unique and pleasing way of presenting such knowledge.

E. L. E.

SURGERY OF THE LUNG. By C. GARRÉ, Professor of Surgery at the University of Bonn, and H. QUINCKE, formerly Professor of Medicine at the University of Kiel. Translated from the German by DAVID M. BANCROFT, M.D. Second edition. Pp. 271; 114 illustrations and 2 colored plates. New York: William Wood & Co.

THE first edition of this work appeared in 1903, and since that time surgery of the lung has made such rapid progress that it has been necessary for the authors to alter and rewrite the subject matter to a considerable extent. Not only by constant and careful elaboration of the older methods of procedure have the operations then in vogue been more frequently, and, on the whole, more successfully carried out, but new methods have been invented and new indications laid down.

The authors very properly devote the opening chapters to a review of the topographical anatomy of the lung, and then discuss the all-important question of pneumothorax, the avoidance and treatment of which has been responsible for much of the advance in thoracic surgery.

In detailing the various methods of maintaining a difference of pressure, mention is made of the work of the pioneers in this field, whose original ideas have been followed by the brilliant discoveries of the investigators of the present day. The advantages and disadvantages of positive and negative pressure, and of the cabinets, apparatus, or masks producing the same, are described very concisely. It is frankly admitted by the author that a greater number of operations on the lung have been performed by him without than with the aid of differential pressure apparatus. As intratracheal anesthesia has been adopted so generally since the publication of this volume, further discussion of its safety and of its numerous advantages is unnecessary. The methods employed in general surgical technic and the treatment of pulmonary injuries and suppurations are brought up to date, and are well worth reading in view of the large number of recent contributions dealing with injuries of the lung occurring in the present war.

The treatment of pulmonary tuberculosis by artificial pneumothorax has become so general that the chapter devoted to this subject is of particular interest. The matter has been considered carefully in every detail and the technic accurately described. It would seem, however, that more emphasis could be laid upon certain of the dangers which may follow the production of the pneumothorax, particularly as many believe that the technic is simple and that preliminary training is unnecessary. The authors rightly conclude that statistics of the results of treatment with artificial pneumothorax are of little value because the condition of the patient was and always will be too diverse. Thus it becomes a question of how long the patient might have lived without the operation.

Trendelenburg's operation on embolism of the pulmonary arteries, the progress made of late years by the operative treatment of rigidity of the thorax in pulmonary emphysema, and the treatment of foreign bodies are all described, indicating that the volume includes the most recent measures employed in thoracic surgery. The work contains much information of interest to the practicing physician, and will prove to be of marked value to the operator accustomed to dealing with the difficulties arising in this new field of surgery. J. S.

WOUNDS OF THE THORAX IN WAR. By J. KEOGH MURPHY, M.D. Pp. 156; 19 illustrations and 2 plates. London: Oxford Med. Press, 1915.

WOUNDS of the thorax, produced by a great variety of weapons and missles, present unusual and difficult problems that civil practice does not prepare a surgeon to solve. The author supplements his large experience by studying the records of the Boer War, particularly the writings of Colonel Sir G. H. Makins. The volume deals with the clinical features of the various wounds, their immediate and remote effects and especially with therapeutic measures. The modern plan of treatment formulated by Sir Watson Cheyne, and that of Cheatte, Fildes and Rajschman are described as well as a summary of Sir Almoth Wright's recent conclusions regarding vaccine therapy. G. M. L.

NOTICE.—In the review of "Serology of Nervous and Mental Diseases," by D. M. Kaplan, published on page 902 of the June issue of the JOURNAL, note should have been made in the title that the book is published by W. B. Saunders Company, Philadelphia and London.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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Pyloric Exclusion.—LEWISOHN (*Surg., Gynec. and Obst.*, 1916, xxii) says the vast majority of surgeons agree that pyloric exclusion ought to be added to gastrojejunostomy to insure the permanent cure of pyloric and duodenal ulcers. There still exists, however, a great difference of opinion as to the best method of accomplishing this exclusion. Lewisohn carried out a series of experiments on dogs to determine, particularly, the value of the following modification of Biondi's method: After the gastro-enterostomy is done, the gastro-hepatic ligament is ligated in the pyloric region, which enables us to deliver the pylorus in front of the abdominal wall. A transverse incision through the seromuscularis is then carried around the pylorus. The muscularis is peeled away from the mucosa which is thus exposed intact for about one inch. The mucosal tube is ligated above and below with a silk or Pagenstecher ligature, cut in between the ligatures and the stumps carbolized. The stumps are then buried by suturing over them the previously reflected seromuscularis layer. Lewisohn concludes that with the exception of Eiselsberg's unilateral exclusion and the modified Biondi method none of the different methods of exclusion guarantees a permanent exclusion of the pylorus. An absolute though temporary exclusion of the pylorus provides for a permanent cure of pyloric and duodenal ulcers. The most simple method from a technical standpoint is the exclusion stitch (Kelling-Berg-Cackovic). This stitch should be used in preference to the more complicated methods (Wilms, Parlavecchio, Biondi). The Eiselsberg's method and the modification of the Biondi method, though guaranteeing a permanent exclusion, are technically too complicated and should not be used. The clinical results are just as good in using the most simple method (exclusion stitch) as in the use of the most complicated method (Eiselsberg). The exclusion stitch is, therefore, the method of choice for the treatment

of pyloric and duodenal ulcers. It is carried out as follows: A double Pagenstecher linen suture, armed with a needle, is carried around the posterior stomach wall, and is held in place by taking several bites in the anterior wall of the stomach. The suture is then tied and the pylorus thus occluded.

Rectal Drainage of Appendiceal Pelvic Abscess.—SCHRAGER (*Surg. Gynec. and Obst.*, 1916, xxii, 482) reports 4 cases in which appendicular pelvic abscesses were drained by the rectum. In 3 of the 4 cases the collections of pus were secondary to a preceding operation for appendicitis and needed most dependent drainage. All 4 cases did very well after the rectal drainage was provided. Some of these abscesses if left alone will perforate into the rectum and thus be cured. He says that rectal examination is a valuable aid in the diagnosis of acute inflammatory processes of the lower abdomen. A number of cases of acute appendicitis are either associated with or followed later on by pelvic abscesses, some of them pointing into the rectum. Rectal drainage of appendicular abscess is a simple procedure and can be resorted to in emergencies even by less experienced surgeons. Cases of suppurative appendicitis convalescing badly occasionally do so because the dependent abscess is not drained. In desperate as well as suitable cases, rectal drainage is a very gratifying procedure. Dr. Ochsner's technic was given as follows: Either gas or ether may be used, although in adults gas is preferable. The patient is placed in the lithotomy position well brought down over the edge of the table. The sphincter is next dilated until it is completely paralyzed. Ether is more suitable for this step than gas. Two long-bladed, right angle, flat retractors are next introduced into the rectum, depressing the upper and lower rectal walls. If the diagnosis is correct, the fluctuating mass soon appears in view, being covered by a smooth, shining rectal mucosa. A small incision is made with scissors or knife in the anterior rectal wall and a sharp pointed forceps, dressing forceps, or the blade of scissors is introduced through this button hole. A rubber tube is then inserted high up into the rectum while another one is introduced into the abscess cavity, thus preventing the feces from entering into it. The tubes escape or are removed in a few days and there is no after-treatment.

Loose Bodies in the Knee-joint.—HENDERSON (*Amer. Jour. Orthop. Surg.*, 1916, xiv, 265) classifies these bodies into (1) fibrinous loose bodies; (2) bodies composed of organized connective tissue, *e. g.*, bone and cartilage, intrinsic in origin; (3) loose foreign bodies, extrinsic in origin. The fibrinous bodies have been variously named according to their size, as melon seeds, rice bodies, wafer bodies, etc. They are not confined to joints, but are often seen in bursæ and in tendon sheaths, and are thought to be pathognomonic of tuberculosis. An hypertrophied fat tag may cause trouble, but Henderson has rarely seen such a case and in none of the cases which he reports was the operation done for the relief of such a condition *per se*. Organized connective tissue loose bodies produce mechanical derangements. They are usually

spoken of as being cartilaginous, but frequently on section there will be seen a flake of bone. In Henderson's experience the majority of these bodies have arisen from the internal condylar surface of the femur. They may be further subdivided into (*a*) those having as their etiological factor some disease such as osteoarthritis or Charcot's disease, and (*b*) those due to injury. Both kinds are inseparable in certain cases. A comparatively slight trauma might produce a loose body in a person affected with osteochondritis dissecans, whereas the same trouble in a normal person would not be productive of trouble. Because it is difficult to determine the degree of indirect trauma necessary to produce the loose bodies in this group, they had better be considered as due to trauma rather than to an actual disease. Trauma, direct or indirect, is essential to the production of a loose body. Surgery offers the only permanent relief, and the general condition of the patient being satisfactory, the bodies should be removed.

Preoperative Treatment of the Hands.—WHITING and SLOCUM (*Ann. Surg.*, 1916, lxiii, 608) conducted investigations at the German Hospital, Philadelphia, to determine a method of hand sterilization that would approach the ideal, be simple in application and allow of more rapid execution. As a result of these investigations they concluded that none of the various solutions used will destroy all germs of the skin in all instances, but that a solution of acetone, alcohol, and one of the coal tar disinfectants of a high phenol coefficient is more efficient than any other agent they have used for skin sterilization. In such a solution the acetone (dimethyl ketone) acts as a solvent of the fatty or oily material of the skin and thus aids in exposing the bacteria to the germicides. The alcohol acts as a solvent; it has the power to penetrate into the cracks and crevices of the skin, as claimed by Braatz, through its ability to destroy and remove small particles of air that may be present; it is germicidal in solutions as weak as 30 per cent., according to Post and Nicoll, in solutions ranging from 40 per cent. to 95 per cent., according to the findings of the authors, with its strongest germicidal powers in solutions ranging from 60 per cent. to 70 per cent., according to Leedom-Greene; it also acts as a good vehicle. The coal tar disinfectant that may be used acts simply as a powerful germicide, destroying all bacteria with which it comes in contact in a length of time varying with its coefficient and the degree of dilution. Patients do not complain of any irritation following the use of this solution, although it causes a burning sensation when used on the scrotum. It does not stain the skin. It reduces to a minimum the time consumed in preparing the field of operation, and its method of application is the simplest. It may be used on a wet or dry skin when necessary. There is no exfoliation of the skin as after iodine nor is there any blistering. It is suggested that a solution consisting of 35 per cent. acetone, 1 or 2 per cent. of a coal-tar disinfectant of a high coefficient, preferably phenoco, with enough alcohol to make 100 per cent., would answer the purpose best. The method of application consists in rubbing the field. of operation for two minutes with a piece of gauze saturated with the solution after either a wet or dry shave. A warm, cleansing tub bath is, of course, always advisable when not contraindicated.

Final Results in Twelve Cases of Colectomy.—Clark (*Surg., Gynec. and Obst.*, 1916, xxii, 533), in referring to Lane's most recent book on intestinal stasis, says that it is not the occasional brilliant result that counts in a work of this unusual character, but it is the analysis of all of the cases that have come under the operator's care, with full histories and a painstaking follow-up record system, that permits the reader to bring his own judgment to bear on this very important subject. In only 6 of the 12 cases operated on, by Clark, may one consider the result as entirely satisfactory. In all cases there has been great improvement in the constipation for a time, to be followed at variable intervals in four by a gradual recurrence of the constipation. In some cases this has not been so severe as formerly, whereas in others it is quite as intense. Roentgen-ray examinations in 3 cases showed in 2 decided dilatation of the ileum to a size closely resembling that of the colon. In none of these cases has there been diarrhea of long standing, and none that was not controlled by simple medicinal measures. In none of the cases has there been undue thirst. In 6 cases there has been marked improvement in nutrition. In the remainder there was no visible effects so far as physical improvement is concerned. As a final summary of these cases, Clark feels that total removal of the colon is justifiable only in severe cases of obstructive constipation. From his experience in these 12 cases he is of the opinion that a less radical procedure must be employed, and inclines to the limitation of the colectomy to the ascending and the middle of the transverse colon, with a lateral anastomosis of the ileum into the transverse colon. In this way the omentum is preserved, and there is less traumatism to the mesentery, with its very important sympathetic nervous system. Any form of anastomosis between different segments of the colon or between the cecum and sigmoid flexure, with the expectation of diverting the fecal current into this new channel, will almost invariably be doomed to failure. Finally, he believes that the one valuable point gained in the study of his cases of colectomy is that the ileum will not uniformly assume the vicarious function of the colon, and that the backward pressure from the colon, through the anastomotic opening, when it is low down, in definite proportion of cases causes dilatation and permanent impairment of the ileum. If a technic can be devised that will prevent the reflux into the ileum it will serve a splendid purpose in obviating one of the objections to an extensive colectomy. In severe cases of obstructive constipation it may be a very efficacious operation if carefully restricted and may be added to our therapeutic list. The immediate danger of the operation and the serious sequelæ that may follow weeks or months later make it, however, too hazardous to extend it into wider fields so ardently advocated by Lane and his enthusiastic followers. It may be efficacious, but it possesses no miraculous function.

THERAPEUTICS

UNDER THE CHARGE OF

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Influence of Some Drugs Used in Treatment of Gout.—DENIS (*Jour. Pharm. and Exper. Ther.*, 1915, vii, 601) says that sodium benzoate, atophan and the salicylates including aspirin, when given in sufficiently large amounts cause an increased elimination of uric acid from the blood. This effect lends some support to the view that the good effects produced by the drugs at present considered by clinicians as most efficient in the treatment of gout may in part at least be due to a power possessed by them of producing a lowered kidney threshold for certain specific substances. Atophan and the salicylates possess this power in a marked degree. Benzoic acid when administered in large doses (8 gm. per day) increases the uric acid excretion in the urine and decreases the uric acid content of the blood. Cinnamic acid in the comparatively small doses used (4 to 6 gm. per day) have little, if any, effect. Quinic acid and colchicum have also no effect on the uric acid elimination. The same is true of para-oxybenzoic acid which shows none of the power possessed by its homologue, salicylic acid, of producing a lowered kidney threshold for uric acid. None of these drugs produce any change in the non-protein nitrogen content of the blood. Benzoic acid, aspirin and atophan were found to have no effect on the creatin content of the blood.

The Uric Acid Solvent Power of Urine After Administration of Piperazin, Lysidin, Lithium Carbonate and other Alkalies.—HASKINS (*Arch. Int. Med.*, 1916, xvii, 405) found that piperazin can cause the urine to dissolve more uric acid than it would without the drug, and this effect is most marked if sodium citrate or bicarbonate be also given and if diuresis be avoided. Lysidin can act as a uric acid solvent but is not a practical therapeutic agent because of the large doses required. Lithium carbonate is a uric solvent if large enough doses are used, but is unsafe and possesses no advantage over sodium citrate or bicarbonate. Sodium citrate and bicarbonate are reliable and satisfactory uric acid dissolving agents when given in such dosage as to keep the urine alkaline.

The Standardization of Digitalis and the Potency of American-grown Digitalis.—ROWNTREE and MACHT (*Jour. Amer. Med. Assn.*, 1916, lxvi, 870) relate their investigations which strikingly emphasize the need of standardization of digitalis. Variations in lethal dose from 6.6 to 19 c.c. per kilogram weight, approximately 300 per cent., were found in the infusions prepared from digitalis leaves of different sources. This difference is greater than should be tolerated by the

profession. The different leaves tested by the authors were all obtained from very reliable sources, and in all probability greater variations exist in leaves purchased in the open market. The authors emphasize that standardization reveals the strength of the digitalis preparation and permits of graded dosage—more or less—according to the potency of the preparation. The physician's duty to his patient does not end with the prescribing of digitalis. Plainly it is incumbent on him to secure digitalis effects if the case is a suitable one. This is more likely to be accomplished if the potency of the preparation is known. It is especially interesting at this time to find that certain American-grown digitalis leaves yielded a product superior in potency to those made from English and German leaves.

Remarks on Bacillus Welchii in the Stools of Pellagrins.—HOLMES (*Arch. Int. Med.*, 1916, xvii, 453) says that B. welchii has been found with marked regularity in the stools of pellagrins in numbers greater than normal. These pellagrins were on a dietary composed principally of vegetable foods high in carbohydrate content. The diet was extremely low in protein and especially in protein of animal origin. Holmes notes the facts that diarrhea is one of the most constant symptoms of the disease known as pellagra and that B. welchii has been found to produce severe diarrhea in children and adults in the presence of a high carbohydrate diet. Furthermore, diarrhea caused by B. welchii can be cured by a protein and buttermilk diet. The author calls attention to the fact that Goldberger has prevented pellagra by the addition of proteins and buttermilk in the diet, and has experimentally caused pellagra by means of a pure carbohydrate diet. He believes that the above facts by no means prove that B. welchii is the direct or sole cause of pellagra but believes their coincidence is sufficiently significant to justify further observation.

Venesection as a Therapeutic Measure.—LAWRENCE (*Bost. Med. and Surg. Jour.*, 1916, clxxiv, 203) says that venesection performed under proper indications, is not a dangerous measure, especially since the "dose" can be accurately controlled. In the presence of dilatation of the heart, renal toxemia, hypertension or a combination of these conditions, it may be expected to act more promptly and more surely than drugs. It lowers blood-pressure and at the same time produces a more efficient circulation when performed in cases of hypertension, but does not, in therapeutic "doses" lower normal arterial tension. Venesection should never be performed in the absence of definite indications, but should not be withheld until the hope of success from any measure is gone. The amount of blood to be withdrawn is to be decided by the point at which relief is to be obtained. The error is generally on the side of removing too small an amount. Repeated blood-letting, when indicated, does not seem to have any ill effects upon the composition of the blood.

Corpus Luteum Extract in the Nausea of Pregnancy.—HIRST (*Jour. Amer. Med. Assn.*, 1916, lxvi, 645) reports encouraging results with the hypodermic administration of corpus luteum extract for the treatment of nausea occurring in pregnancy. He bases this treatment on the

presumption that there is more than a coincidence between the formation and disappearance of the corpus luteum of pregnancy and the cessation of the nausea. Only five cases are reported, four of which were successfully treated. Hirst makes this preliminary report in the hope that this treatment may be tried by others in order to determine whether or not it is of value.

Pellagra—Causation and a Method of Prevention.—GOLDBERGER (*Jour. Amer. Med. Assn.*, 1916, lxvi, 471), in a summary of his observations made in three institutions where pellagra was endemic, states that a diet containing a liberal amount of fresh animal and leguminous protein foods, without other alteration in the hygienic and sanitary conditions, successfully prevented the annual recurrence of the disease in practically 100 per cent. of the cases. Of the 209 cases of pellagra observed at the two orphanages during the spring and summer of 1914, not less than 172 completed at least the anniversary date of their attack under observation. In only one of these 172 cases, following the change in diet, was there recognized evidence of a recurrence, although on the basis of experience elsewhere, from 99 to 130 might reasonably have been expected. Nor was any new case observed among the non-pellagrin residents, 168 of whom completed not less than one year under observation. Of the group of pellagrins on the modified diet at the insane asylum, 72 remained continuously under observation up to October 1, 1915, or at least until after the anniversary date of their attack of 1914. Not one of this group has presented recognizable evidence of a recurrence, although, of a group of thirty-two controls, fifteen have had recurrences. Pellagra may, therefore, be prevented by an appropriate diet without any alteration in the environment, hygienic or sanitary, including the water supply. At an isolated convict camp, previously free from pellagra, with an average population of from seventy to eighty white males, eleven volunteers were segregated and, after a preliminary observation period of two and a half months, placed on an abundant but one-sided, chiefly carbohydrate (wheat, corn, rice) diet, from which fresh animal proteins and legumes were excluded. At least six of these volunteers developed pellagra. This result would appear to have been brought about by the diet on which they subsisted. A definite conclusion as to the intimate mechanism involved in bringing about or in preventing the disease by diet cannot be drawn from the available data. For the practical purposes of preventive medicine it would seem to be of fundamental importance to recognize that the pellagra-producing dietary "fault" is capable of correction or prevention by including in the diet suitable proportions of the fresh animal and leguminous protein foods.

The Intraspinal Administration of Mercurialized Serum.—HUNT (*Jour. Am. Med. Assn.*, 1916, lxvi, 404) reports a series of 45 cases of which 40 were given intraspinal injections of mercuric chlorid, and 5 were given sublamin injections. These patients were at the same time given intramuscular injections of mercuric salicylate every week, and in the very early ones intravenous injections of salvarsan. The cases treated comprised cases of tabes, general paresis, cerebrospinal

syphilis, taboparesis, clinical tabes (tabes with a negative serology) and syphilitic hemiplegia. These patients were observed over a period of six months and Hunt believes that the number of cases is too small and the period of observation too short to draw any definite conclusion. The author found that the reaction from mercuric chlorid or sublamin in no way differed from the reaction which followed the administration of salvarsan. The sublamin did not seem to give the same reduction in the cell count or clinical improvement as did the mercuric chlorid. No ill results followed these injections. The three deaths could be easily accounted for, as the patients were practically moribund at the time of the treatment, and were given the injections as a last resort. The patients with tabes and cerebrospinal syphilis were helped more than any others. The ten patients with general paresis treated showed less improvement than almost any of the others. One-half of them showed no change and two became worse. Such improvement as did occur was evident in the feelings of the patient, in the sphincter control, in the pains, in the gait, and in the serology. There was no improvement in the reflexes. Such intraspinal treatment can be given only at intervals of two weeks, because a cell count does not fall sooner. The reaction obtained was one in which the cell count was first greatly increased and then diminished. The cell count and the globulin yielded much sooner than did the Wassermann.

The Treatment of Central Nervous System Syphilis.—WALKER (*Boston Med. and Surg. Jour.*, 1916, clxxiv, 195) summarizes the treatment and results in the first 40 cases of central nervous system syphilis at the Peter Bent Brigham Hospital. This group includes cases of tabes, general paresis, cerebrospinal syphilis and syphilitic meningitis; cases of purely cerebral syphilis are excluded. In the treatment of parasyphilis three methods were employed: one, salvarsan, intravenously alone; another, the Swift-Ellis method; and a third, salvarsanized serum alone intraspinally. Walker used large doses of salvarsan intravenously for those cases treated with salvarsan alone; in those treated with serum intraspinally 20 to 25 c.c. of undiluted serum were used. It was found that cases of syphilis of the central nervous system with only a positive blood react well to salvarsan; those with a positive blood and spinal fluid may react well to salvarsan alone, but they do much better when intraspinal serum is used in conjunction with salvarsan, and some who do not react to salvarsan alone do react well to the combined method. One may obtain improvement in general paresis with the combined treatment. Cases of syphilitic meningitis may clear up with salvarsan alone but the combined treatment is the quickest. Cases of central nervous system syphilis with a negative blood and positive spinal fluid findings react readily to salvarsanized serum intraspinally alone, even when salvarsan intravenously has failed. The spinal fluid of the cases treated with salvarsan has become negative in two cases, whereas the spinal fluid of seven cases treated with the serum alone has become negative. The author feels that salvarsanized serum is a great asset in the treatment of syphilis of the central nervous system, and in the general run of cases he thinks

the Swift-Ellis method is of great value and that this method in conjunction with mercury given intramuscularly is the best treatment of syphilis of the central nervous system at the present time. Marked improvement always follows such treatment.

The Comparative Pharmacological Action of Ethylhydrocuprein (Aptochin) and Quinin.—SMITH and FANTUS (*Jour. of Pharm. and Exper. Ther.*, 1916, viii, 53) call attention to some facts regarding optochin which are important because of the increasing use of the remedy for the treatment of pneumonia. Optochin is an alkaloid derived from cuprea bark and in its chemical structure is closely related to quinin. While quinin chemically is methoxycinchonin, optochin is a hydroxycinchonin. Morgenroth, in 1911, reported that he was able to protect over 90 per cent. of animals against artificial pneumococcus infection by injections of optochin. His work has been confirmed by others and particularly of late many favorable reports have been made regarding its therapeutic use in lobar pneumonia. The authors found that the pharmacological action of optochin is qualitatively like that of quinin, but differs in degree. Optochin is more toxic than quinin. In view of its considerable degree of toxicity, the authors urge caution in the clinical use of optochin, especially in its intravenous administration. They found that when administered intravenously it lowers the blood-pressure somewhat less than quinin although it depresses the heart more. The peripheral vasoconstriction probably counteracts partly the effects of cardiac depression. Optochin was not so efficient an antipyretic as quinin in experimental fever of animals. Optochin has been advocated for local use in eye infections, particularly those due to the pneumococcus, but the authors found that even a 2 per cent. solution was highly irritant to the conjunctiva.

The Treatment of Typhoid Fever by Intravenous Injections of Polyvalent Sensitized Vaccine Sediment.—GAY and CHICKERING (*Arch. Int. Med.*, 1916, xvii, 303) report a series of 53 cases of typhoid fever, in which the diagnosis was absolutely certain both on clinical and on laboratory grounds, treated by intravenous injections of a sensitized polyvalent typhoid vaccine. These patients were cared for under varying conditions in private houses and hospitals. The mortality in these cases has been precisely what one would expect under the best hospital conditions (9 per cent.), which the authors regard as suggesting that, under uniform conditions, with their method of treatment the mortality would have been less than the average. The mortality has been composed, to a large extent, of what may be termed "accidents" of typhoid, namely 60 per cent. of deaths by hemorrhage or perforation. Their method of treatment has consisted in the intravenous injection of $\frac{1}{50}$ to $\frac{1}{25}$ mg. (150 to 300 million bacteria) of a sensitized, polyvalent, killed typhoid vaccine sediment prepared after the method of Gay and Claypole. This injection gives rise to a series of symptoms characterized particularly by a chill, rise and fall of temperature, and leukopenia followed by hyperleukocytosis. The fall of temperature with its attendant hyperleukocytosis leaves the patient at least temporarily benefited, and the benefit and normal temperature may be

permanent. Thus in 66 per cent. of the cases a distinct benefit was obtained, as shown by lowered temperature, disappearance or amelioration of subjective symptoms and an apparently accelerated recovery. In 41.5 per cent. of this 66 per cent. the recovery was of an abortive form with a critical fall of temperature and a permanent normal temperature established within a few days. This permanent normal temperature was reached on an average seven days after beginning treatment in these cases. There remains, however, 34 per cent. of cases which are classified as relatively unaffected. They regard this classification as underestimating the beneficial results for reasons given. In none of the cases did the use of the vaccine have any apparent harmful effect on the case, although in four, in which too large a dose was used, the symptoms were somewhat alarming. A series of subcutaneous injections following the intravenous treatment apparently aids in preventing relapses. The authors regard the mechanism of benefit and cure in these cases which were affected by the treatment as due to a combination of specific hyperleukocytosis and the presence of antibodies in the patient's blood. The injection of vaccine could be shown in a number of cases to be followed by the disappearance or diminution of bacteremia and usually also by an increase in the Widal. In those cases which did best the Widal was originally high and those cases which showed the least effect had the low Widals. The cases judged as "mild" before treatment began did better on the whole than those regarded as "severe." There were, however, a number of severe cases which showed abrupt recovery or benefit. On the hypothesis that successful results are due to the strength of the antibodies already established in the patient, Gay and Chickering ventured in severe cases with low antibody content, to combine with the vaccine treatment the intravenous injection of considerable amounts of typhoid immune serum from goats. These cases, although few in number, suggest that this type of treatment with further elaboration might increase the percentage of favorable results. They regard the use of sensitized vaccine as being better for intravenous injection than plain typhoid vaccine or less specific methods of treatment that have been suggested by other authors, owing to the fact that sensitized typhoid vaccine produces a specific form of hyperleukocytosis of maximum degree (Gay and Claypole), and may also be shown to be followed by an increase in active immunity of the patient against the disease.

The Intravenous Administration of Mercury in Syphilis.—Shaw (*Med. Record*, 1916, lxxxix, 823) reports 16 cases of syphilis treated by intravenous injections of mercuric chlorid with good results. The dose used was $\frac{1}{8}$ to $\frac{1}{6}$ of a grain to a patient of 140 to 150 pounds body weight, every five to seven days. Shaw says that this method is quick, safe and certain; the dose can be very accurately measured and the administration is free from pain. The therapeutic effects are just as quick, in many cases more certain and more permanent than those following salvarsan and neosalvarsan. This method is recommended also because of its availability and cheapness. The administration is attended with no untoward results except for a low grade of phlebitis which may produce obliteration of the vein used and which is in proportion to the concentration of the solution used.

PEDIATRICS

UNDER THE CHARGE OF

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The Schick Test in an Orphan Asylum.—STEARNS S. BULLEN (*New York State Jour. Med.*, 1916, xvi, 208) reports the results of the Schick test on 132 normal, healthy children at the Rochester Orphan Asylum. Of this number, 100 were again tested one year later. On both occasions the toxin was diluted with normal saline solution, so that the required amount ($\frac{1}{50}$ minimum lethal dose for the guinea-pig) was contained in 2 c.c. The children averaged from two to seventeen years in age. The injections were attended with practically no pain or distress. On both tests practically 55 per cent. of the children gave a negative reaction, showing that they had sufficient natural antitoxin in their tissues to neutralize the toxin injected, that is, at least $\frac{1}{30}$ unit per cubic centimeter of serum, sufficient to protect against diphtheria. Immunization was attempted on 41 children, with strongly positive reactions, by injecting subcutaneously, on two occasions with a four-day interval, $\frac{1}{4}$ c.c. of a toxin-antitoxin mixture. Of this number 35 still remained in the asylum eleven months later, and on being again tested still gave strongly positive reactions, showing they had developed little if any antitoxin as a result of the treatment. Eighteen children who gave positive reactions in May, 1914, showed no reaction in April, 1915. Fifteen children who gave no reaction at the first test showed more or less strongly marked reaction at the second test. Positive or negative results with this test do not give us data which remain the same for an indefinite period of time, one or two months at the outside being the limit. The test, which should be repeated at least once a month during an epidemic, in conjunction with the singling out of "carriers" by throat culture, allows epidemics in institutions to be controlled at about half the expense for antitoxin and with much less discomfort to the children.

Nephritis without Albuminuria.—J. PORTER PARKINSON (*Brit. Jour. Child. Dis.*, 1916, xiii, 138) reports a case of pneumonia in a boy, aged three and one-half years, which was followed by all the signs and evidences of nephritis, except that no albumin could be found in the urine at any time. Seven days after an uneventful recovery from the pneumonia he developed extreme swelling of the face, arms, hands, feet, legs, and the wall of the trunk. There was no sign of fluid in the chest or abdomen. Daily examination of the urine showed no albumin, but a few hyaline and granular casts and an occasional red corpuscle. The daily amount of urine was normal and contained fairly abundant urates. The blood-pressure was 90 mm. After four days of hot-air baths and purgatives the edema began to disappear, and in ten days all casts and blood had disappeared from the urine, and a week later

the case was discharged as cured. The author believes the case to have been one of acute nephritis without albuminuria, but not probably induced by the pneumococcus which usually shows severe hematuria and abundant organisms in the urine which were absent in this case. The majority of cases of nephritis with edema and without albuminuria seem to be a result of scarlet fever, but in this case there was only an acute pneumonia. The absence of albumin in such cases causes many of them to be overlooked in the absence of careful microscopic examination. From the reports of Ballico, Herbert and others, cases showing casts and erythrocytes and no albumin may show no other signs of nephritis or may show only headache, pallor and fatigue. The author calls attention to the report of Philippe, in 1864, who claimed 60 cases of scarlatinal nephritis in which no albumin appeared, and the thesis of F. Leonetti, 1914, who reported a number of cases of nephritis in English soldiers with all the clinical signs except albuminuria.

Factors in the Incidence and Fatality of Measles.—J. G. WILSON (*Arch. Pediat.*, 1916, xxxiii, 261), from a study of statistics, shows that the mortality from measles is less than was considered correct some years ago. In New York City, in 1913, the mortality rate was 2.15 per 100, and in 1914 the rate for 28 States and Territories was 1.73 per cent., so that at present the case mortality rate of measles throughout the United States is less than 2 per cent. This, however, represents the low-water mark of measles mortality, as indicated by the mortality statistics compiled by a large insurance company two years ago, which showed a much higher mortality than has prevailed since the compilation was made. The mortality rate in measles is almost uniformly higher in institutions than in private practice and runs from 13 per cent. to 30 per cent. in large institutions generally. The Contagious Disease Hospital at Ellis Island showed a mortality from measles of less than 10 per cent. before the war, and for the last three months only 8.5 per cent. It is evident, therefore, that the disease has no fixed mortality rate, due probably to some as yet undetermined factor. A regular, periodical recurrence of measles epidemics has been noted in many cities, the time interval being about two years in New York City. The theory of the successive susceptible crops of individuals will not explain the periodicity of epidemics which is shown to vary in different places. Only one factor seems to bear a causal relation, and that is overcrowding. Suppurative otitis media, bronchopneumonia, and cross-infection are noted as the most important complications. Data are taken from the hospital at Ellis Island, and cover 2000 cases of measles. During a period of three years measles was four times as frequent as all the other contagious diseases combined. The influence of season on the development of bronchopneumonia seems small. Generally speaking every recovery from measles and bronchopneumonia is balanced by a death from measles with some other complication.

The Wassermann Reaction in Mental Deficiency in Children.—ALFRED GORDON (*Arch. Pediat.*, 1916, xxxiii, 273), in a study of 78 cases presenting mental defects of varying degrees, makes the following points as regards hereditary syphilis: Even in the absence of all external evidences in child and parents, every case of mental abnormality in

children should be investigated from the stand-point of hereditary syphilis. When hereditary syphilis causes extensive deformities or actual malformations of the central nervous system or other organs therapeutic endeavors are baseless and in vain. But when there is only feeble-mindedness of various degrees, and when this is associated with epilepsy, tremors or choreiform movements, or frequent and persistent headaches or where there are neurotic phenomena such as outbreaks of anger, of violence or tendency to vicious habits, then encouraging results may be obtained from methods based on the newer serologic investigations. In the series of 78 cases comprising imbeciles, idiots and feeble-minded with epilepsy, petit mal, headaches and those without functional or organic disorders the Wassermann test showed that 50 per cent. presented a positive reaction. While syphilis causes permanently defective offspring it also causes mental deficiency which is amenable to improvement. The detection of such recoverable cases is of paramount value. A negative Wassermann result should be followed by repeated tests at intervals. A positive result should be followed by vigorous and prolonged treatment by antisyphilitic remedies. Children up to the age of five were given mercurials and iodids. From that age on the treatment commenced with neosalvarsan, then continued with mercury and the iodids. The intraspinal method of salvarsanized serum was used exclusively on children of fifteen and sixteen years and supplemented by mercury and iodids. Mercury was given exclusively by inunction. The cases with organic changes were unresponsive. The feeble-minded showed decided improvement, in some, epileptic attacks diminished or ceased, those with petit mal especially showed improvement and the mentality in all these functional conditions showed striking improvement. The most striking improvement was in the feeble-minded with no functional disturbance.

GYNECOLOGY

UNDER THE CHARGE OF

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Ultraviolet Rays in the Treatment of Pelvic Inflammation.—A few months ago we discussed in this department some work done by Fromme, of Berlin, in the treatment of chronic pelvic inflammatory conditions by means of ultraviolet light from the mercury vapor lamp. A recent report of similar work carried on in New York has recently been published by HELLMAN (*Am. Jour. Obst.*, 1916, lxxiii, 662), a former pupil of Fromme. The technic was apparently identical: the apparatus used is the "künstliche Hohensonnelampe" designed by Bach and Nagelschmidt; the source of light is a "transparent quartz tube, $\frac{8}{12}$ cm. long, on the ends of which are two transverse

tubes which contain the mercury electrodes. The electrode vessels are provided with fan-shaped coolers with which the heat loss and therefore the current consumption is regulated. On each electrode between the coolers is situated the beaded lead which conducts the current to the lamp." The latter is enclosed in a suitable container, by means of which the amount of light permitted to pass can be regulated, the whole being easily adjustable up and down. The quartz glass used is of such quality as not to absorb any of the ultraviolet rays, upon which the therapeutic effects are believed to depend. The patient is placed before the lamp in a reclining position, the part of the body to be rayed being exposed, and the rest covered with a thin sheet. The eyes of the patient and of any one else in the room must be protected by dark glasses. The exposures vary from a minute and a half, with the lamp at a distance of 75 cm. at first, to twenty minutes at a distance of 40 cm. after a couple of dozen treatments have been given. Usually at least a day is allowed to intervene between two treatments; it is generally found that brunettes can stand longer exposures at the beginning than blondes.

Hellman reports the results in 8 cases of pelvic inflammation; all these were treated as ambulatory patients, without any other therapeutic measures. All eight have been examined recently and are apparently well, but only a short time has elapsed since the completion of treatment. While admitting that these eight, with the twenty-five cases previously reported by Fromme, are much too few from which to draw any definite conclusions, the author considers that "they do show however, that with this harmless technic some astounding results have been claimed and that these results are worthy of investigation whenever this kind of material presents itself. Certainly this mercury-quartz lamp should be tried in every case of pelvic inflammation of the subacute and chronic variety before operation is advised, and especially if the more commonly known methods have failed." In the discussion which followed the presentation of this paper before the Obstetrical and Gynecological Section of the New York Academy of Medicine, the majority of the speakers emphasized the marked improvement that is often seen in cases of this sort in time if let alone, and not subjected to too much meddlesome local treatment; if it does nothing more than accomplish this end, the light treatment may be of real value, although it cannot be denied that it may have a stimulating effect on the circulation and thus tend to aid in the resorption of exudates and diminution of inflammatory processes.

Tuberculin Treatment of Renal Tuberculosis.—Notwithstanding the fact that surgeons of experience are practically unanimous in the opinion that medical treatment has no place in tuberculosis of the kidneys, provided the diagnosis is definitely made while the case is in an operable stage and there are no special contraindications, the profession as a whole is as yet apparently far from being convinced upon this point. A recent report by HYMAN (*Jour. Am. Med. Assn.*, 1916, lxvi, 1379) upon the treatment of genito-urinary tuberculosis with Rosenbach's tuberculin is therefore of considerable interest. In 1910 Rosenbach described a new tuberculin, and reported a number of successful results of its application in the treatment of surgical tuber-

culosis, and since then several articles have appeared in the German literature substantiating Rosenbach's claims. Only one case had been described, however, in which the treatment was used in renal tuberculosis, and the report upon this was too meagre to permit of any conclusions being drawn. Hyman therefore undertook in a series of 13 cases of postoperative and of inoperable tuberculosis of the genito-urinary organs to try out this substance, which is a product of the symbiosis of the tubercle bacillus and the Tricophyton holosericum album. Its toxicity is considerably less than that of other tuberculins, so that much larger doses may be given. It is injected either locally into the diseased part or subcutaneously in an initial dose of from 0.01 to 0.1 c.c. this amount being successively increased by 0.1 c.c. unless a severe reaction ensues. As a rule injections are given every three to seven days, according to the severity of reaction produced. The maximum dose should not exceed 1.5 c.c., a total of 40 to 60 c.c., generally constituting the course of treatment. Of the 13 patients treated by Hyman, only 2 showed any improvement whatever; all the others were absolutely unimproved, and a few developed additional tuberculous foci during the course of treatment. The cases comprised for the most part patients upon whom nephrectomy with or without ureterectomy had been performed for renal tuberculosis; in one there was a tuberculous condition of the adnexa, and in others tuberculosis of other portions of the male or female genito-urinary tract in addition to the renal tuberculosis.

Bacteriology of Chronic Ovaries.—Following out the same line of thought as his well-known investigations into the possible specific bacterial etiology of such conditions as cholecystitis and appendicitis, ROSENOW (*Jour. Am. Med. Assn.*, 1916, lxvi, 1175) has carried out some rather interesting experiments with regard to the causation of certain ovarian conditions. In his previous work, Rosenow claims to have obtained from a number of cases of cholecystitis, appendicitis, etc., organisms which when injected into animals reproduced the same character of lesion, and no other; hence the author's deduction that certain organisms may bear some specific relation to the causation of certain inflammatory conditions of hitherto obscure etiology. While this work has not been definitely confirmed or accepted as yet, it must be considered an extremely interesting attempt to throw some new light on old problems. In studying the possible bacterial etiology of certain ovarian lesions, Rosenow has made cultures from 64 specimens of ovaries removed at operation for the most part because of typical chronic "fibrocystic degeneration;" only a small proportion of the cases gave a history of previous acute pelvic infection, and in only 3 cases was there present a relatively acute process. In a number the history indicated clearly that the pelvic disturbance began after the contraction of a severe cold during the menstrual period or following definite attacks of tonsillitis. The technic used in making the cultures was the same as that employed in the earlier work, shake-cultures from one or more pieces of ovary, at least 1 cm. in diameter, being made in tall columns of ascites-dextrose agar. Of the 3 cases with acute tubo-ovarian abscesses, 2 showed pure cultures of Streptococcus viridans and the third of gonococci. In 10 cases the cultures were

sterile. In the remaining 51 cases streptococci were found in 29, only 7 of these showing pure cultures, however. Of the other organisms encountered, Welch bacilli were present in 21 cases, diphtheroid bacilli in 10, a few colonies of Staphylococcus albus in 9, gonococci in 2, colon bacilli in 3, and an aërobic streptothrix in 1. The tubes were cultured in 5 cases, and when positive showed organisns with cultural characteristics similar to those from the ovary. The staphylococci and diphtheroid bacilli are considered by the author as accidental or harmless invaders, whereas the significance of the Welch bacillus is doubtful. It probably, however, plays no determining role in the etiology of fibrocystic ovary. Intravenous injections into animals of 5 of the strains of streptococci showed them to be of a low grade of virulence, rabbits and dogs recovering promptly. Two of these strains appeared to show, however, an elective affinity for the ovary in these animals. The first of these was obtained from a girl, aged eighteen years, with an imperforate vagina, fibrous degeneration of the tubes with closure of the right, and fibrous and cystic degeneration of the ovaries. All cultures from the tube remained sterile, while those from the ovary showed streptococci. A subculture was injected into a female dog, which was chloroformed three weeks later; the ovary showed a number of encapsulated, yellowish nodular areas beneath the capsule, filled with chocolate colored fluid, rich in leukocytes, but sterile on culture. There were no other lesions. The second case was that of a woman, aged thirty years, who developed subsequent to an acute arthritis severe dysmenorrhea and menorrhagia, for which first the left and then the right ovary were removed. Cultures from both showed the Streptococcus viridians; subcultures were injected into 3 dogs and 4 rabbits and the animals killed on the second and third days. All showed severe lesions of one or both ovaries, such as hemorrhages and leukocytic infiltration. Cultures from the ovaries showed streptococci in about half the cases. Five of the animals showed in addition to the ovarian lesions distinct arthritis and other miscellaneous lesions. From these investigations, Rosenow considers the conclusion warranted that fibrocystic degeneration of the ovary, even in the absence of previous acute infection, may be due to a low grade hematogenous infection by streptococci having an elective affinity for these structures. If this be true, it seems possible that the timely eradication of primary foci of infection might in some cases prevent the premature sclerotic degeneration of the ovary.

OTOLOGY

UNDER THE CHARGE OF

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Supramastoideal Pneumatocele in Chronic Mastoiditis.—O. Muck *Ztschr. f. Ohrenheilk.*, January, 1916). A pneumatocele, in the region

entitled, implies a circumscribed space between the periosteum and bone, containing air and extending upward and backward as well as forward from the mastoid surface exteriorly; the result not of injury but of the passage of air from the pneumatic cells of the mastoid, through some defect in the cortical bone, beneath the periosteum elevating it from the bone to varying extent. The author finding no example in the literature of the subject of such a pneumatocele containing the gaseous products of decomposition, reports the following case: The patient, aged four years, had chronic suppurative otitis media of three years' standing; two days previous to examination he had severe pain in the ear, and within twenty-four hours the development of a marked fluctuating swelling behind the auricle extending from 3 to 4 cm. upward and backward. A crescentic incision at the base of the auricle, posteriorly, revealed a decided thickening of the soft tissues and extension of the incision through the periosteum liberated, not pus, but a foul-smelling gas; the scalp was found to be elevated upward and backward, and in the pocket thus formed there were small blood coagula evidently not of recent origin. The cortical surface of the mastoid was pale, without areas of congestion or spontaneous defects. The diploetic interior of the mastoid was, in places, of a light green color without granulomata, the amtabos was in place but the malleus wanting, and there was a large obstructive granulation polyp in the tympanum and a small quantity of greenish-yellow fetid pus in the mastoid cavity. The plastic dressing followed the operation in a fortnight, and the case was entirely healed in seven weeks. There being in this case no spontaneous defects in the mastoid cortex, there being no sutura mastoidea squamosa and no fistulous leakage of pus through the cortex, the only conclusion possible was that the gases engendered in the diploetic spaces of the mastoid had made their way along the normal vascular bone openings outward to the cortical surface and denuded it of its periosteal covering. The preoperative palpation of the postaural swelling, which was apparently provocative of considerable pain, gave the impression of a fluid content.

Otological Report of One Year of Military Service.—Oscar Mauthner (*Monatschr. f. Ohrenheilk.*, December, 1915). The number of cases treated in the ear, nose, and throat department of the Garrison Hospital, No. 6, in Olmutz, in charge of the author, as regimental surgeon, in the first year of the war was 5097, a number equaling that of many polyclinics in time of peace; but the character of the service rendered was essentially different in two respects, and divisible naturally, in two directions, that of estimation of condition and of possible results, as bearing upon capacity for future service, on the one hand, and treatment, on the other, the patients being further divisible into those who came into the hospital because of injuries inflicted by weapons in the hands of an enemy and those whose complaint was the result of the peculiar conditions incident to war. The functions of the department would therefore be: (1) examination, diagnosis and classification; (2) diseases of the ear, including the nose and throat, under conditions incident to war; (3) wounds of the ear, nose, and throat incident to war. Under the first heading came not only the determination of the character of the disease but also an estimation of its degree

as bearing upon the serviceableness of the patient, and whether the disease was acquired before or after and during the entrance into service. The number of cases in which there was already existing disease, or in which this had been acquired by other means than that of wounding, proved to be considerable, amounting to somewhat more than 2000 cases, resulting properly from the fact that the acute demand for service had necessitated the calling out of so many men ordinarily beyond service years. The largest number of cases classified as unfit were those suffering from chronic suppurative disease of the middle ear, including nearly 50 per cent. of those patients examined in the ear, nose, and throat department of the hospital and determined unfit for service. Multiplied by the number of military subdepartments carrying on the same work, there is evidence of an unexpectedly large number of men withdrawn from service to the State by this disease. The chronic suppurative disease of the middle ear is in a very large percentage of the cases not only the result of an acute infection, but is distinctly a *morbus paupurum*, and the importance of the increase of institutions in which this disease can be treated and the people taught the necessity of its prevention is distinctly emphasized. Treatment of these cases under the conditions of military service is usually impossible except insofar as operative measures are concerned, and these not infrequently find, and leave, the patient unfitted for return to duty except in some subordinate capacity at the rear. Even when the chronic middle-ear suppuration has come spontaneously to an end, the resultant chronic adhesions and thickening cause an impairment of the hearing in so high a grade as to interfere with the patient's value for active service. Next to the suppurative middle-ear diseases as a cause of unfitness come the results of acute and chronic infectious diseases, foremost among which has been found to be syphilis, 1 per cent. of all the cases unfit for active or secondary service being due to this disease. Of the total examined, including the cases rejected on account of diseases of the nose and the throat, about 60 per cent. of the cases presented at the hospital for examination were declared as fully fit for service. Among the causes of aural complications other than those resulting from wounds, typhus was the most prominent, it having been the author's observation that suppurative inflammation of the middle ear not only occurred frequently in typhus, but that it was often one of the initial symptoms, an observation confirmed by members of the medical staff having charge of epidemic diseases, but contrary to that found in text-books, which placed the complications of the ear in the fourth or fifth weeks of the disease, while in the majority of the cases of this kind under the author's care, by the time the above-mentioned period had been reached, the suppurative middle-ear trouble had become complicated by mastoiditis, demanding operation in 9 cases as compared to 25 operations in cases due to other causes. Diseases of the inner ear and of the auditory nerve were also found to be more common in typhus than in other infectious diseases. Another observation of interest was that of acute inflammation of the middle ear in cholera, intimately presenting the characteristics of a similar manifestation in tuberculosis. A similar middle-ear complication was also observed, but in a much less percentage, in dysentery. The present war has resulted in the publication of a large number of special articles upon injuries to the ear under titles difficult of classification, such as laby-

rinth vibration, detonation deafness, deafness from hand-grenade concussion, gunshot wound of the skull with cochlear symptoms in contradistinction to which the author gives the results of 200 carefully studied cases, dividing them into two classes, direct and indirect, the direct including those in which the force was applied directly to some portion of the ear, the indirect those in which the effective force was expended outside of the ear and still caused distinctly determinable changes in its condition, this complicated organ consisting of some parts which are directly and others only indirectly attackable, it being understood that this differentiation cannot be maintained in all cases, because under certain conditions there may be no injury to the more exposed portion of the organ of hearing accompanied by a concussion effect producing injury in the deeper seated parts, or the direct attack, in addition to forcible disruption of the exterior portions of the ear, may extend also to the labyrinth and auditory nerve, the protected positions of the more important parts of the organ of hearing being such that the outer ear most frequently, the middle ear but seldom, and the inner ear very rarely, was the subject of direct injury. The majority of injuries to the auricle were those resulting from explosions in the immediate neighborhood and burns resulting from explosions, gases, and flames, as well as those cases in which the injury to the auricle was the result of the exposure to intense cold. These injuries were comparatively slight and the resultant deformity was moderate. There were other cases, however, in which the injury to the auricle was very much more severe, including cuts, burns, tearing away of the upper portion of the auricle, and, in one case, the loss of the greater portion of both auricles. More frequent than the wounding of the auricle were the direct wounds of the external auditory canal and of the mastoid process, gunshot wounds of the mastoid process being repeatedly recurring type, and often found in connection with frontal wounds of the skull, the tympanic cavity being either directly or indirectly injured, and in the majority of the cases the labyrinth subjected only to indirect invasion. In this type of cases the projectile entered either through the external canal or its neighborhood, penetrating the mastoid. In some cases the course of the bullet was in the opposite direction. The result of a simple gunshot fracture of the external canal was usually a membranous and bony narrowing, or even complete closure, of the canal, 10 cases of such absolute bony closure having been observed. The determination as to operation in these cases was based upon the amount of remaining hearing and the presence of a suppurative process behind the bony closure; in the latter cases only was operation determined upon, the preferable operation being that in which the auricle was reflected forward, the radical operation being contraindicated in view of a possible return of the hearing. In 2 of these cases, notwithstanding the fact that the hearing power in both of them was, before operation, determined to be relatively good, neither the drum head nor the ossicles could be found. In 4 other cases in which the wounding of the external canal was accompanied by destructive concussion of the mastoid process the sequestræ were removed in the progress of an antrotomy, the destruction of the bony mastoid being so complete as to have left a portion of the dura bare in one instance and to have included the exit portion of the facial canal in another.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Recommendation as to Sanitation Concerning Employees of the Mines on the Rand Made to the Transvaal Chamber of Mines.—W. C. GORGAS (*Jour. Am. Med. Assn.*, 1914, lxii, 1855) reports on his investigations into the cause of the high death rate from pneumonia among the native laborers working in the mines, and recommends measures necessary for the reduction of the death rate and the improvement of the general sanitary condition of the mines and compounds. The death rate of these natives has fallen from 71.7 per thousand in 1902 to 26.84 in 1912; the most prevalent in 1912 being pneumonia, phthisis, meningitis, and enteric fever, their death rates, 9.8, 5.4, 1.3, and 1.1, respectively; but these are much too high as all the employees are men in the prime of life. The death rate from pneumonia is very high among those natives coming from the tropical climate north of latitude 22, being 26.3 for 1912; while a death rate of 8 per thousand among the non-tropicals was comparatively low. A negro having the natural racial low resistance to the pneumococcus, coming from a climate where practically no natural immunity against the disease occurs, and having had but little or no contact with civilization and white man's diseases, into a climate where exposure to cold produces a constitutional depression very favorable for the pneumococcus, is highly susceptible to the disease, especially during the first few months of his employment. These conditions are very similar to those previously existing on the Isthmus of Panama, where the death rate for pneumonia among the black employees of the Canal in 1906 was 18.74 per thousand, which is higher than the existing rate in the Transvaal. In Panama it was found that no particular localities had continuously high rates; the seasonal incidence of the disease was very irregular and inconstant; no difference in the death rates could be determined between the negroes who slept in wet clothes after working in the rain and those who had had a change of clothing; in the barracks the upper bunks were more ventilated and more draughty than the lower, but there is no difference in the mortality of those sleeping above and those below; altitude had but little effect, there being no appreciable difference between the rates in camps at sea level and those at 200 to 300 feet elevation. The only difference in susceptibility was shown to be governed by the length of time the laborer had been on the Isthmus. However, in 1907, the negro laborers were

allowed to leave the barracks provided by the commission and scatter out along the line of the canal, build for themselves cabins on the hills, each with a small cultivable piece of land, so that in 1910, 7000 out of 37,000 lived in their separate establishments with their families. Coincident with this scattering of the negroes there was a sudden and permanent drop in the pneumonia death rate on the Isthmus and it was remained low ever since. The death rates for pneumonia for the succeeding years were as follows: 1906, 18.74; 1907, 10.61; 1908, 2.6; 1909, 1.66; 1910, 1.66; 1911, 3.24; 1912, 1.30. During the first few years on the isthmus the negroes were crowded into barracks, allowing each but thirty feet of floor space. Now it is a well recognized fact in military hygiene that overcrowding of the barracks is coincident with inflammation of the upper respiratory passages which at times becomes epidemic. This was the case in Panama and doubtless is the case on the Rand. Thus the non-immunes in close contact with other negroes would develop such inflammation, which would afford the portal of entry for the pneumococcus, resulting in the high mortality. Inoculation against pneumonia as recommended by Sir Almroth Wright has been attempted with varying degrees of success. It is recommended that the Chamber of Mines continue experimental inoculation against pneumonia using different strains of pneumococci and when vaccinating natives that one-half be kept as controls. The common drinking cups and faucets should be abolished not only as a protection against pneumonia but also against tuberculosis and syphilis. The death rate by tuberculosis is very high; in 1912, 5.65 per thousand by pulmonary tuberculosis as compared with less than 1 per thousand for the same year in Panama. Overcrowding plays as important a part in the spread of tuberculosis as in the case of pneumonia. Disinfection in the dwellings of the tuberculous is useful and important, and the disease may be particularly combated by fresh air, sunshine, cleanliness and roomy quarters. Miners' phthisis can be reduced by laying the dust by the more general use of water-sprayers already used in some parts of the Rand. Cerebrospinal meningitis, which at times causes considerable mortality, can be combated by disinfection and scattering. Typhoid fever can be eliminated by the vaccination of all negro employees, and such of the white employees as so desire. The most serious sanitary defect on the Rand is the housing of the native, as he is allowed in general but fourteen feet of floor space, which forces the occupant into close personal contact, largely increasing the spread of any infectious diseases. Scattering and the construction of simple native huts properly laid out, would not only decrease the spread of infectious diseases but would create a native labor force more stable and continued on account of their being allowed to live with their families. The unmarried native should be allowed at least fifty feet of the floor space in the barracks. In regard to the diet of the employees there is room for improvement as the daily ration consists mostly of mealie meal and a small amount of meat, which the native buys himself, and which is too large a proportion of carbohydrates. On the isthmus the best plan was found to be the supplying of a varied diet to the negroes at cost, to be cooked by the family. Sewage systems should replace the bucket system of disposing of night soil, wherever practicable, and in the mines a fly-proof vault system can be employed

conveniently and economically. All of the fifty-four mines are each entirely independent as to their sanitation and the care of the sick. Sixty-two hospitals, none of which is equipped or manned in a first class manner, treat 2150 patients. If a combination could be effected a much higher state of efficienty could be brought about at no increase of cost. One or a few larger hospitals would permit a centralization of authority, the best surgical appliances, greater accuracy and uniformity in diagnosis, and better control of all diseases. Finally, the establishment of a central sanitary bureau reasponsible to the Chamber of Mines and entirely independent of the management of the individual mines, the head of this department to represent the mines on all sanitary questions, would result in the efficient supervision and control of all matters pertaining to the health of the employees and the sanitation of the mines.

Intestinal Parasites in Children.—GREIL (*Amer. Jour. Dis. Children*, November, 1915) gives the results of the examination of 665 children for intestinal parasites seen by him in Montgomery, Ala. He found that out of 665, 240 were harboring intestinal parasites or a percentage of 36.1 per cent. The varieties of parasites found were: Hookworms, 177 (62 females, 115 males, or 26.75 per cent.); Hymenolepis nana, 38 (20 females, 18 males, or 5.75 per cent.); Ascaris lumbricoides, 27 (12 females, 14 males, or 4.06 per cent.); Oxyuris vermicularis, 5 (3 females, 2 males, or 0.75 per cent.); Trichocephalus dispar, 5 (2 females, 3 males, or 0.75 per cent.); mixed infections, 2 or more parasites, 12 (6 females, 6 males, or 1.8 per cent.). It is not surprising that hookworm should be found the most common, but the large percentages of Hymenolepis nana, and Ascaris lumbricoides and the small number of Oxyuria vermicularis was somewhat surprising, as the latter has been considered quite common, while the hymenolepis were considered comparatively rare. The author believes that every county and municipality in the south should provide a man for special work along these lines and that children should not be permitted to attend public or private schools until after such examination, and the results prove to be negative.

The Prevention of Pellagra.—GOLDBERGER, WARING, and WILETS (*Public Health Reports*, October 22, 1915), give the results of the observations of the effect of certain dietaries upon the recurrence of pellagra in institutions in southern cities. The dietaries of two orphanages were modified, so that they consisted principally of fresh animal and leguminous protein foods. Since the change in diet, there has not been observed any evidence of the recurrence in any of the 67 persons, who, in 1914, had symptoms of pellagra, nor have any new cases been observed among the pellagrins and residents of 1914, 99 of whom had been under observation for not less than one year. In the second orphanage there has been observed only one single indication of a recognizable evidence of a recurrence among 105 persons who had symptoms of pellagra in 1914, nor have any new cases been observed among 69 non-pellagrin residents who had been under observation for at least one year. At the Georgia State Sanitarium, an institution

in which pellagra has been very prevalent, two wards were placed at their disposal, one in the colored female service, and the other for the white female service, in October and December, 1914 for a test of dietaries in a number of pellagrins. The diet in these wards was modified on the same principle as that at the orphanages. The institution routine, hygienic and sanitary conditions were kept unchanged as far as possible to do so. Since the change of diet and up to October 1, 1915, there has not been observed this year any recognizable evidence of the recurrence in any of the pellagrins in these wards, 72 of whom have remained continuously under observation throughout this period, or at least until the completion of the anniversary date of the 1914 attack. During the same period of observation not less than 15 or 47 per cent. of the 32 control female pellagrins have presented recurrences. The authors draw the conclusion that pellagra may be prevented by an appropriate diet, without any alteration in the environment, hygienic or sanitary.

A Milk-borne Paratyphoid Outbreak.—LEVINE and EBERSON (*Jour. Infect. Dis.*, 1916, xviii, 143) report ten cases of supposedly typhoid fever occurred in Ames, Iowa during the early part of November, 1914. The routine diagnostic Widal tests were questionable. A bacteriological study showed that, six to seven weeks after the onset, the sera from the patients tested, were more patent toward B. paratyphosus B than the A type, while B. typhosus was not clumped. Organisms which are indistinguishable from B. paratyphosus, culturally, were isolated from the feces of a carrier suspect, and from the urine of one patient. The occurrence of all the primary cases in a restricted area of the community and on one milk route, the high case incidence among children under fourteen years (70 per cent.); and the location of two possible sources of infection of the milk supply are conclusive that milk was the vehicle of infection. The bacteriological findings indicate that the disease was paratyphoid fever. The outbreak points out the necessity of testing questionable and negative typhoid specimens against the paratyphoid strains.

Insecticides.—CASTELLANI and JACKSON (*Jour. Trop. Med.*, November 15, 1915) give the results of experiments carried out in Serbia on the efficacy or worthlessness of substances used as insecticides, and come to the following conclusions: (1) In regard to solid and liquid insecticides, the substances which we have found to be deleterious to body lice (Pediculus corporis de Geer, 1778) are, in the order of their efficiency, kerosene oil, vaseline, guaiacol, anise preparations, iodoform, lysol, cyllin and similar preparations, carbolic acid solution, naphthalene, camphor. Pyrethrum has a very feeble action on lice; while boric acid, sulphur, corrosive sublimate, and zinc sulphate, when used in powder form, have apparently no action whatever. As regards bedbugs, kerosene oil is the best insecticide. Next to it comes guaiacol, one of the most active drugs of those that were tried. (2) Substances which are powerful licecides may have very little or no action upon bedbugs, and *vice versa*. For instance, iodoform which kills lice within ten to fifteen minutes has

practically no deleterious action on bedbugs, which may live for more than twenty-four hours when exposed to it. It also has very little effect on fleas. Pyrethrum, on the other hand, has a much more powerful action on bedbugs than on lice. (3) For use against lice on a large scale, as among troops and prisoners, perhaps the best insecticide is naphthalene. This substance has a lower licecide action than kerosene oil, guaiacol, iodoform and anise preparations, such as onethol, but it has a less displeasing odor than the first three named, and is much cheaper than onethol powder. In stored blankets and clothing it is also practicable and of use, as frequently lice are found stored through the summer. Naphthalene is useful also for its well-known deterrent action upon moths. We are speaking here of insecticide powders. As regards liquid insecticides, the American Red Cross Sanitary Commission gave sanction to kerosene by its daily use upon troops and prisoners. (4) For the better class of patients in practice, a menthol powder is to be preferred to naphthalene in most cases, as its odor is not displeasing, while it is repellant to mosquitoes, in addition to mice and fleas. Such powder is especially useful in summer and in hot countries, as it has a cooling effect on the skin and often prevents prickly heat.

Anopheles Punctipennis Say.—MITZMAN (*U. S. Public Health Reports*) writes that Anopheles punctipennis say occurs widely in the United States and is found in certain localities where malaria has been investigated. It therefore seems desirable to look more closely into the role of the mosquito as a transmitter of malarial fevers. The only previous work along this line was not considered definite enough to exclude this form as a carrier. An effort was made to make the study as exhaustive as the material would permit although no special attempts were made to simulate the natural conditions. The investigations were limited to subtertian fever and two series of experiments were attempted: one, with recently emerged mosquitoes and a heavily infected carrier undergoing quinin treatment; the other, with older mosquitoes and a lighter human infection, untreated. The anopheles used were bred mosquitoes which emerged August 25–26, 1915. They were kept in lantern chimneys set in deep glass trays, lined with a layer of absorbent cotton, covered with heavy blotting paper and kept constantly saturated with water. A temperature of 21° to 22° C. was maintained. In the first series of experiments, specimens of A. punctipennis were allowed to bite the patient whose blood was examined for the number of gametocytes present among 100 leukocytes. In all he was bitten 664 times and up to the thirty eighth day, the dead or weak mosquitoes were dissected but no infection of the stomach or salivary glands was observed. In the further determination of the possible infectivity of these insects, two healthy persons, whose blood was negative for malaria, permitted these mosquitos to bite them. The mosquitoes were applied from 4 to 180 times but neither person developed malaria. As a control, 14 specimens of A. quadrimaculatus were fed on the same infected person and, as a result, 2 of them showed malarial infection. One of the laboratory force was accidentally bitten by one of these mosquitoes and developed a sharp attack of subtertian fever.

In series 2, older specimens of A. punctipennis, twenty-nine to thirty days, were used to determine if any age difference influenced the susceptibility to plasmoidal infection. The case was one of subtertian malarial fever which had received no treatment and the gametocyte count was taken in this case also. The patient was bitten 158 times by A. punctipennis, 102 times by A. quadrumaculatus, and 6 times by A. crucians. 67 specimens of A. punctipennis were dissected and during a period of thirty-four days, a healthy person was allowed to be bitten 22 times by A. punctipennis. Both of these experiments showed negative results. Out of 60 specimens of A. quadrimaculatus, 8 showed infection and out of 3 of A. crucians, 1 only showed infection.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Spontaneous Arteriosclerosis in Dogs.—As greater attention is given to the question of the distribution of arteriosclerosis the more widely disseminated we find it among animals. However, all animals are not equally affected by it, and in some it appears with great frequency at definite periods in their life. The common appearance of medial degenerations in rabbits has frequently been commented upon, while the relative infrequency of its occurrence in guinea-pigs has also been observed. In horses and cattle, medial and intimal disease of the arteries is also quite common in the older animals. Scleroses of the arteries have been reported in monkeys, pigs, sheep, deer and parrots. Although dogs have been quite extensively used in experimental work, they have not been found very favorable in the study of arteriosclerosis. Investigators using young dogs have mainly reported negative results in their attempts to produce arterial lesions. On the other hand, a number of observers have noted the spontaneous development of canine arteriosclerosis. Koellisch found vascular sclerosis in 10 out of 50 working dogs and 13 out of 50 pet dogs. This would suggest that the hard work imposed upon dogs on the continent has no influence in bringing about scleroses of the arteries. STRAUCH (*Ziegler's Beiträge* 1916, lxi, p. 532) examined 56 dogs, 47 being under five years of age and 9 from five to fifteen years. These dogs were of a variety of kinds including lap dogs. Of the animals under five years, there were only

3 showing a mesaortitis and 1 with a small nodular area suggesting early arteriosclerosis. The lesions which he describes as mesaortitis appear to represent a degenerative process. The author draws attention to fine ridges which normally appear in the branches of the aorta and are sometimes mistaken for early scleroses. Of the 9 dogs ranging in age from five to fifteen years, there were evidences of arterial lesions in every one. The aorta was most frequently affected. Arteriosclerosis appeared in the aorta in 7 cases while a mesaortitis appeared in 3. Other large vessels were also occasionally attacked. The scleroses appeared in the intima in the form of diffuse or nodular thickening. The medial degeneration was associated with the laying down of calcium salts. The author was struck by the similarity of the arterial lesions in dogs with those occurring in man. This conclusion appears to be entirely based on the finding of splitting of the internal elastic lamina. A very decided difference from the human sclerosis is the absence of fatty change of either the intima or media.

Atheroma and Other Lesions Produced in Rabbits by Cholesterol Feeding.—Bailey (*Jour. Exper. Med.*, 1916, xxiii, p. 69) carried out an interesting study on feeding egg yolk and cholesterol to rabbits. In many respects his work substantiates the findings reported by others, but also brings out some important features on the disposal of excessive cholesterol in the tissues. The cholesterol and egg yolk were fed to rabbits by mixing them with their daily ration of food. A control animal to which no cholesterol was given but which received large doses of cotton seed oil was also observed. Where cholesterol was fed, cotton seed oil was used as a solvent. The experiments were carried on over a period of from thirty to three hundred and forty-eight days. Eleven of the 15 animals showed definite lesions in both the aorta and pulmonary artery. These consisted of small raised yellowish white spots and streaks close under the inner lining. These spots showed the presence of large cells with fat containing droplets which were anisotrophic. Associated with the accumulation of these cells was a proliferation of fibroblasts and fine elastic fibers. This observation is important in indicating a possible pregnancy of the changes induced. Occasionally a fatty degeneration appeared in the media. He also observed the deposition of fatty materials in the liver. In part this was found in the liver cells as well as in Kupffer cells. This fat also contained cholesterin. He observed cirrhosis in the liver of 6 rabbits. The kidneys of 8 rabbits showed definite macroscopic change. This consisted of yellowish-white streaks arranged radially in the outer zone of the medulla. These streaks were due to a deposit of anisotropic fat within interstitial endothelial cells. These cells appeared to be associated with the lymph spaces. Although some cholesterin fat appeared in the cells of the tubules it was in very small quantities and did not give rise to the macroscopic appearance. The large vessels of the kidney showed but little change in their structure. There appeared to be some relation between scarring of the kidney and the deposit of the cholesterin fat. These scars are similar to those that are not uncommonly found in rabbits. The adrenal was not infrequently found much enlarged. It is probable that the adrenal has some function in the storage and metabolism of the cholesterol. The author believes that the anisotropic fat in the liver produces a cirrhosis.

Immune Reactions against Tumor Growth in Animals with Spontaneous Tumor.—"While the conditions determining the growth of tumors in experimentally inoculated animals has been studied extensively, the conditions underlying the growth of tumors in animals with spontaneous growths are to a great extent unknown. An analysis of these factors in the latter class of animals is of special theoretical and indirectly also of practical interest in as much as such animals correspond to human beings affected by cancer. The investigations are intended as contributions to the analysis of this problem." In thus indicating their problem the authors, FLEISHER and LOEB (*Jour. Med. Research*, 1916, xxxiv, p. 1), compared the rapidity of growth of inoculated tumors in mice already possessing spontaneous tumors with that in normal animals. They also observed the activity of immunity present in normal mice against tumor inoculation to that present in animals with spontaneous tumors as well as the effect upon the spontaneous tumor of the inoculation of another neoplasm. Some interesting conclusions were obtained in this study. It was found that mice with spontaneous tumors do not offer as good a soil for the growth of inoculated tumors as normal controls. The same mechanisms which inhabit tumor growth in normal animals appears in mice with spontaneous tumors. They have further confirmed their previous conclusions that mice with spontaneous tumors are better soil for the ordinary spontaneous but otherwise not readily transplantable tumors than control mice. It was found, however, that those tumors which can be readily transplanted into normal mice also readily take when inoculated into animals with spontaneous tumors. The spontaneous tumors grow best in those animals in which they have originated. This, they believed, was due to a specific condition present in the animal in which the tumor originated, and is not so available in normal mice. After the extirpation of spontaneous tumors, substances which antagonize the growth of an ordinary transplantable tumor were not demonstrated. They believe that spontaneous tumors in contradistinction to transplantable tumors do not produce any considerable quantity of immune substances comparable to those produced by the ordinary transplanted tumor, nor do spontaneous tumors neutralize immune substances produced through the growth of transplantable tumors.

An Experimental Study on Sporotrichosis.—In 1912 D'AGATA (*Lo Sperimentale*, 1915, lxix, 697) isolated the sporotricium Beurmani from a granuloma of the jaw. He was able to isolate the organism in culture and by this means to identify the type. Subsequently he studied the nature of the infection in mice and rats. These animals were inoculated subcutaneously and intraperitoneally. In each he observed the development of granulomatous nodules, and he was able to recover the microorganisms from the lesions. In the peritoneum small nodules were scattered over the surfaces of the various viscera. In the early stages, the tissue reaction consisted of a migration of leukocytes to the infected area followed by an endothelial and fibroblastic proliferation. The central portion subsequently showed necrosis but the leukocytes persisted in and about the necrotic material. The organisms were found

in the periphery of the necrosis where many endothelial and giant cells were developed. Fibroblasts were found in the outer zone of the nodule around which lymphoid and plasma cells were also seen. Nodules were also present in the liver, spleen and other organs. These had a similar structure. A full description of the tissue changes is given by the author.

Notes on Certain Anaërobes Isolated from Wounds.—In this study ROBERTSON (*Jour. Path. and Bact.*, 1916, xx, p. 325) obtained cultures from gangrenous wounds received in battle. She was able to isolate a variety of anaërobic bacteria, and classified them according to their reactions on media. Four groups of anaërobes were recognized: (*a*) rauschbrand group; (*b*) perfringens group; (*c*) non-liquefiers of gelatin; (*d*) proteolytic group. The majority of cultures belonging to either the B. perfringens type or the proteolytic type represented by B. malignant edema (Koch). It was not uncommon to have more than one anaërobe in the same wound. Although the author has followed a uniform method for classifying these anaërobes the findings are not conclusive that the grouping can be used in the broad classification of these organisms. In her work she has almost entirely disregarded similar studies made in America.

NOTICE.

ARMY MEDICAL CORPS EXAMINATIONS.

The Surgeon-General of the Army announces that preliminary examinations for the appointment of First Lieutenants in the Army Medical Corps will be held on July 17, 1916, and August 14, 1916, at points to be hereafter designated. Full information concerning these examinations can be procured upon application to the Surgeon-General, U. S. Army, Washington, D. C. The essential requirements to securing an invitation are that the applicant shall be a citizen of the United States, shall be between twenty-two and thirty years of age, a graduate of a medical school legally authorized to confer the degree of Doctor of Medicine, shall be of good moral character and habits, and shall have had at least one year's hospital training as an interne, after graduation. Applications must be completed and in possession of the Adjutant-General at least three weeks before the date of examination.

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Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *provided the request for them be written on the manuscript.*

All communications should be addressed to—

DR. GEORGE MORRIS PIERSOL, 1913 Spruce St., Phila., Pa., U. S. A.

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